NOV 21 1925

Medical Lib.

BULLETIN

OF THE

JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XXXVII, No. 5 NOVEMBER, 1925

Contents

The Histological Changes Brought About in Cases of Exophthalmic Goitre by the Administration of Iodine. WILLIAM FRANCIS RIENHOFF, JR. 285

Studies on the Biology of the Streptococcus erysipelatis. III. Experimental Production of Erysipelas in Rabbits and Demonstration of Protective Power of Immune Erysipelas Sera. KONRAD E. BIRKHAUG 307

Congenital Duodenal Septum with Obstruction. S. M. SEIDLIN. 328

Congenital Cysts of the Lung. AMOS R. KOONTZ 340

Books Received 362

Book Reviews 365

PUBLISHED MONTHLY

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, U. S. A.

INFANT DIET MEAD'S MATERIALS

Individualized Infant Feeding

There are more babies fed on fresh cow's milk than any other artificial food.

A vast majority of these babies are fed according to the physician's instructions to the mother.

A large number of these physicians use *Dextri-Maltose* as the modifier.

MEAD'S INFANT DIET MATERIALS

are appreciated by all physicians interested in pediatric work.

It is well worth while to every physician to write for our *Pediatric Tool Kit.*

The Mead Policy

Mead's Infant Diet Materials are advertised only to physicians. No feeding directions accompany trade packages. Information in regard to feeding is supplied to the mother by written instructions from her doctor, who changes the feedings from time to time to meet the nutritional requirements of the growing infant. Literature furnished only to physicians.

MEAD JOHNSON & COMPANY, Evansville, Indiana, U. S. A.
Manufacturers of Infant Diet Materials

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

Copyright, 1925, by The Williams & Wilkins Company

The Histological Changes Brought About in Cases of Exophthalmic Goitre by the Administration of Iodine[1]

By William Francis Rienhoff, Jr.
Assistant Surgeon, The Johns Hopkins Hospital

THE existence of a close relationship between endemic goitre and iodine has been recognized for many years. As long ago as 1820 Coindet (1) reported that goitre could be reduced in size by the administration of iodine. In 1852 Chatin (2) called attention to the high incidence of goitre in localities where the amount of iodine was low, and maintained that endemic goitre could be prevented by the ingestion of iodine. In 1863 Trousseau (3) administered tincture of iodine by mistake for tincture of digitalis in a case of exophthalmic goitre, and noticed subsequently a striking clinical improvement. Following this period there was a lapse of about thirty years during which the use of iodine in the treatment of goitre had fallen to a great extent into disrepute, until Baumann (4), in 1896, discovered that iodine was normally present in the thyroid gland, being held in organic combination. Following this discovery many interesting observations were made by Baumann, Oswald (5), and Roos (6), the most important of which are as follows: (*a*) Ingested iodine is stored in the thyroid gland; (*b*) if iodine is withheld, a compensatory hypertrophy of the thyroid gland occurs, this being the first allusion to the relationship of the iodine content to the histological structure of the gland; (*c*) the iodine content of the thyroid gland is directly proportional to the amount of colloid present; and (*d*) in colloid goitre the percentage of iodine is relatively far below that of the normal gland.

It was not until 1907–1909, however, when Dr. Marine (7) and his coworkers took up the systematic study of the thyroid gland, that we obtained any definite data as to the relationship between the iodine content of the gland and its histological structure. Marine (7), Williams, and Lenhart studied physiological hypertrophies of the thyroid gland in animals, and came to the conclusion that involution of these hypertrophies to the resting or colloid state could be brought about by the administration of iodine. A study of post-operative conditions and of postmortem specimens in man led them to the conclusion that all thyroid hyperplasias are anatomically, chemically, and biologically the same.

[1] Presented before the 127th Annual Meeting of the Medical and Chirurgical Faculty of the State of Maryland, Baltimore, April 30, 1925.

As a result of their work the prevention of simple or endemic goitre by the administration of minute quantities of iodine is now being brought about in many parts of the world. Their investigations were directed, as was stated above, principally towards the discovery of the etiology of simple goitre and its prevention, but they also found that in exophthalmic goitre the percentage of iodine in the gland is inversely proportional to the hypertrophy and hyperplasia present.

In the last two years Plummer and Boothby (8), and Means (9) in the United States, and Fraser (10), in Great Britain have again employed the use of iodine in cases of exophthalmic goitre. The clinical results obtained from the use of iodine in exophthalmic goitre in the Johns Hopkins Hospital will be published in detail by Dr. H. M. Thomas, Jr., and myself in a later paper. It may be said, however, that our observations go to prove that iodine is a very valuable drug in the pre-operative preparation of ninety-five per cent of the cases of exophthalmic goitre.

The purpose of the present paper is to report briefly the histological changes noted in the thyroid gland in cases of exophthalmic goitre before and after the administration of iodine. Three successive cases, in all respects clinically typical, were studied. Brief reports of them are as follows:

The first case was in a man aged 36, who gave a history of good health until four months previously. At that time he noticed loss of weight, tremor of the hands, increasing appetite, exophthalmos, and a tumor of the neck. Palpitation was present, with dyspnoea and tachycardia; he felt weak and very nervous and had frequent attacks of diarrhoea. Examination showed a nervous, undernourished man with a weak, high voice, a moist brownish pigmented skin, and fine hair. The von Graefe, Moebius, von Stelwag, Dalrymple, Rosenbach, and Jaffroy signs were definitely positive. There was marked exophthalmos. The cervical lymph glands were enlarged. The lateral lobe and the isthmus of the thyroid gland were diffusely enlarged. A marked thrill and bruit were present at the superior and inferior poles. There was slight retromanubrial dulness, the relative cardiac dulness was increased, the heart rate was 160. Blood lymphocytes 32.6. The basal metabolism +58. Under local anaesthesia a portion of the right upper pole was excised. The specimen was fixed at once in Zenker's solution and formalin. Serial sections were cut in paraffin after staining with hematoxylin and eosin. After this operation the basal metabolism, on being repeated, was +58. The patient was given Lugol's solution, ten minims four times a day, for three weeks. After the first week the basal metabolism fell to +50, the second week to +49, and the third week to +17. After this period double partial lobectomy was done. The gland was at once fixed in Zenker's solution and formalin. Serial sections were cut in paraffin and stained with hematoxylin and eosin. The postoperative basal metabolism was +3.

The second patient was a girl of 19. There had been an insidious onset two years previously, when the patient noticed that she tired easily and was irritable and nervous. There was profuse sweating and tremor of the hands, and she also had an enormous appetite. There was loss of weight. The patient had on examination extreme exophthalmos, with hypertension. The skin was oily. The von Graefe, Dalrymple, Stelwag, Moebius, Jaffroy, and Rosenbach signs were positive. There was tremor of the lips, tongue, and hands, and moderate enlargement of the heart. The thyroid isthmus and both lobes were diffusely enlarged. An apical systolic thrill and murmurs were present, and the heart rate was 140. The basal metabolism was +55. At the first operation the right upper pole was excised, and was immediately fixed in Zenker-formalin solution. Following excision the basal metabolism was +55.

Lugol's solution, ten minims three times a day, was given. After the first week the basal metabolism was +17; after the second week, +5. The second operation was a double partial lobectomy. The gland was fixed immediately as in the first case. The post-operative basal metabolism was +7.

The third patient, a woman aged 31 years, had been well until the present illness. Swelling of the throat was first noticed 7 months previously. She was nervous and emotional; she had lost weight, and tremor of the hands was present. On examination the patient was found to be very sick and apprehensive; she was undernourished and had an oily skin. There was diffuse enlargement of the thyroid isthmus and of both lobes. Apical thrill and bruit were present. Exophthalmos was marked. The von Graefe, Stelwag, Dalrymple, Rosenbach, Moebius, and Jaffroy signs were positive. The basal metabolism was +51. There was tachycardia, the rate being 140; retromanubrial dulness was definite, and relative cardiac dulness increased. The right upper pole was resected under local anaesthesia. The post-operative basal metabolism was +51. Lugol's solution, ten minims three times a day, was given. After one week the basal metabolism was +23, after the second week +14. At operation a double partial lobectomy was done. The basal metabolism was ∓0. The gland was fixed immediately in Zenker-formalin as in the two preceding cases.

Over a year ago I noticed in operating upon patients with exophthalmic goitre who had been treated with iodine that there was a vast difference between the gross appearance of the thyroid gland in these cases and in those in which iodine had not been given. The gland in the former cases seemed to be quite definitely increased in size and hardened in consistence. The capsule was thickened and seemed to be bulging with the contained lobulated parenchyma. On incision, the gland in certain areas was more resistant to the knife, the lobulation being much more pronounced, and the gland as a whole seemed considerably less vascular than those from clinically similar cases in which iodine had not been administered. The most striking change noticed, however, was that from the glairy cut surface there fairly dripped a clear lymph-like fluid which I assumed to be colloid secretion of the gland. Furthermore, there were small cyst-like areas appearing in the gross specimen, suggesting beginning adenomata, which were also full of this fluid resembling colloid. In short, the gland in the patients who had not received iodine was much more vascular at operation and on section gave the typical beefsteak appearance which is so common in exophthalmic goitre, whereas the gland in the patients having received iodine was less vascular, more fibrous, seemed to contain more colloid, and frequently showed small cystic areas.

I next compared the histological structure of the gland in a series of 15 cases in which no iodine had been given and in an equal number in which it had been used. The striking difference in the histological structure of the gland was at once apparent, but because of the varied histological pictures that one may encounter in cases of exophthalmic goitre, I thought it would be interesting to compare the histological structure of the gland before and after the administration of iodine. This was done, as described above, in the brief reports of the three typical cases of exophthalmic goitre. The tissue was immediately placed in Zenker-formalin, at the operating table. It was fixed and then cut in both paraffin and celloidin. A series of blocks was cut from all parts of the

gland in each case and a series of sections was cut from each block. The sections were stained with hematoxylin and eosin.

The microscopical pictures for all three cases, both before and after the use of iodine, will be described in detail, but inasmuch as the histological structure and the changes are identical in all the cases, one description will suffice for the three.

Examination of a series of sections made from the excised right upper pole, before the administration of iodine, revealed the following histological picture (Figs. 1 to 6). They presented the characteristic histological picture of exophthalmic goitre. Everywhere the gland was divided into lobules by a fibrous-tissue stroma enclosing dilated blood vessels and lymphatics containing large droplets of colloid. There were also numerous collections of small lymphocytes in the intralobular stroma throughout the sections. The stroma was delicate, but even so was definitely increased above the normal. One was struck with the marked increase in the parenchyma of the gland in comparison

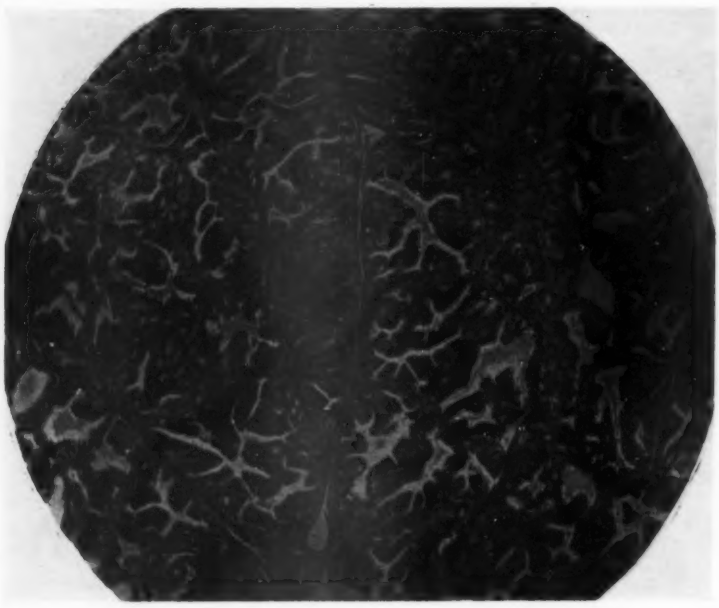

FIG. 1. Low power, 16 mm. lens. Ocular 4 ×—magnification, 40. One of the series of sections from excised right upper pole. Case 1. Before administration of iodine. Classical histological structure of exopthalmic hypertrophy of thyroid gland. Marked increase in parenchyma and decrease in open or colloid spaces. Fibrous tissue increased above normal. Lobulation of gland clear, showing large central acinus with smaller peripheral acini. Some lobules of solid epithelial cells. No colloid in smaller acini and very little in large acini. Acinus in lower right quadrant full of desquamated epithelial cells.

with the equally pronounced decrease in the open or colloid-containing spaces. In some areas the lobule was a solid mass of epithelial tissue in acinar formation with very little, if any, colloid present. The acini that were patent and the colloid-containing spaces appeared to be very irregular in form and size, suggesting an almost lace-like structure. The colloid was very scant, absent in many acini, and when present stained very poorly and irregularly. In some acini it was extremely vacuolated and shrunken. Occasionally acini were seen which contained large numbers of desquamated epithelial cells and red blood cells. The epithelium was everywhere elevated to a high columnar type, and the walls of the acini were folded in upon themselves in papillomatous-like ingrowths. The lobules showed an arrangement, originally described by MacCallum (11), in which the large acini lay towards the center of the lobule and the smaller ones towards the periphery. Whether these small acini were new growths of acini, or whether they were simply a section across one of the pseudopodia-

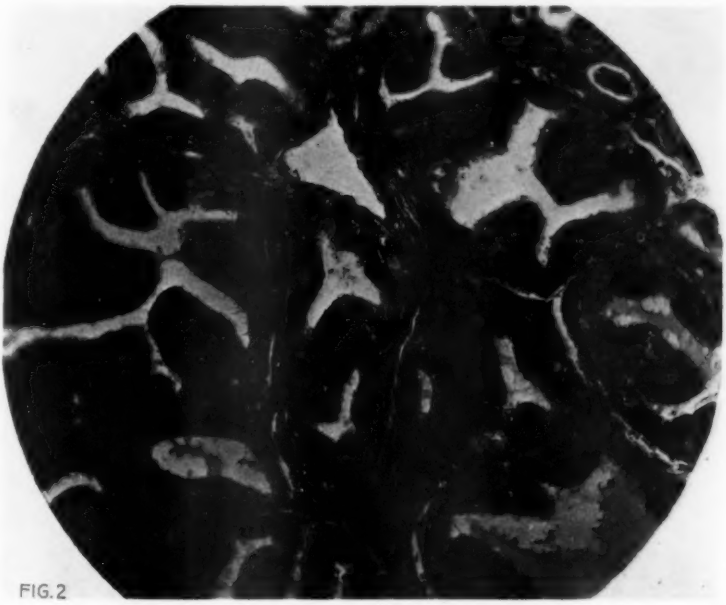

FIG. 2

FIG. 2. High power, 4 mm. lens. Eye piece 4 × —176 magnification. Higher magnification of Fig. 1. Dilated blood and lymph vessels in stroma. Highly refractile, clear areas between acini in lymphatics represent colloid being carried away from gland. Appears about six thirty in Fig. 2. Acini thrown up in folds like papillomata. High columnar epithelium. Large, clear, vesicular nuclei. Epithelium not abutting colloid but abutting on empty space produced by retraction of colloid away from epithelial edges. Vacuolization of colloid very evident.

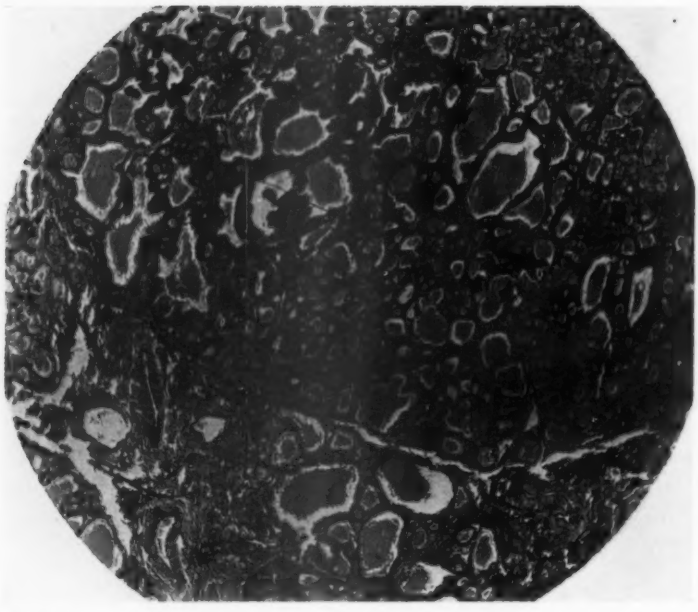

FIG. 3. Low power, 15 mm. Eye piece 4 × —magnification, 40. Case 2. Right upper pole before iodine was administered. Case not quite as marked clinically and histologically as Case 1. Slightly more colloid than in Fig. 1. Epithelial ingrowths and elevation very pronounced. Fibrous scars more pronounced. Otherwise descriptions of Figs. 1 and 2 apply to Fig. 3.

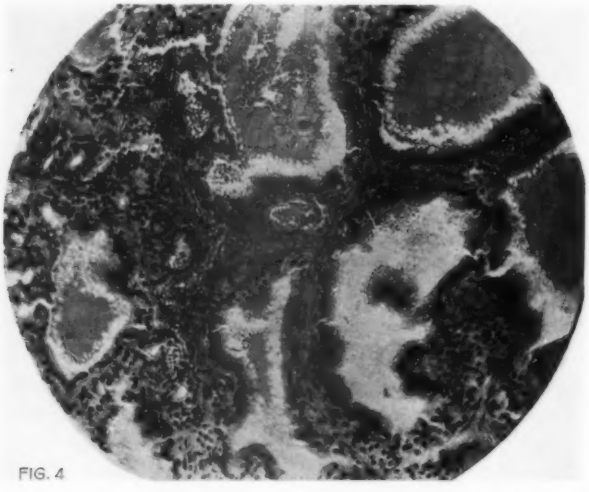

FIG. 4

FIG. 4. High power, 4 mm. lens. Eye piece 4 ×—magnification, 176. Before iodine. Higher magnification of Fig. 3. More colloid present than in Fig. 1 and 2. Case not as sick as Case 1. Colloid vacuolated and shrunken away from edge of epithelium lining acinus. Epithelium high, columnar and infolded into acinus. Peripheral distribution of small acini in lobule. Stroma increased. Epithelial cells and red blood cells in acini.

like processes of the deformed large acinus, could not be determined. These small acini were often made up of only three epithelial cells without any evidence of a lumen. The epithelial cells lining the larger acini were tall columnar and almost bulging with very large, clear and vesicular, enclosing rather large chromatin granules. Frequent mitotic figures were encountered. The cytoplasm was somewhat mottled in appearance, and this mottling seemed to be due to the presence of a clear colloid sub-

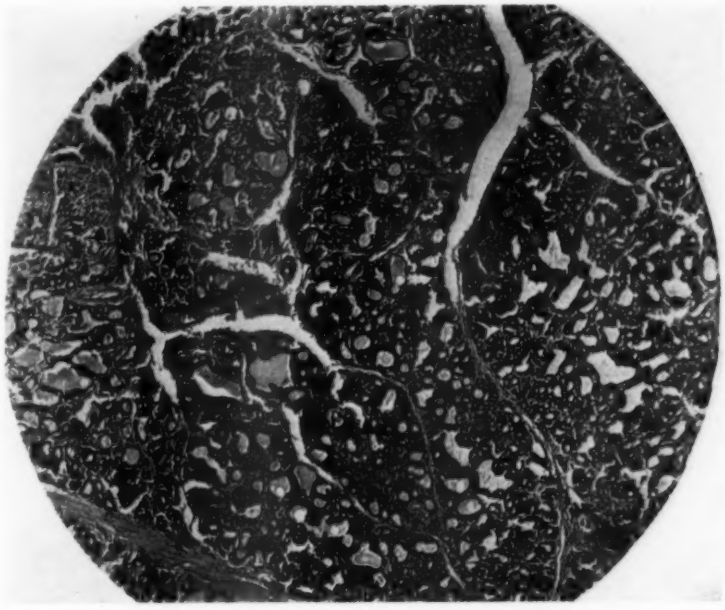

FIG. 5. Low power, 16 mm. lens. Eye piece 4 ×—magnification, 40. Case 3. Before iodine was administered. Right upper pole. Fig. 5 more typical of exophthalmic hypertrophy than Fig. 3, but not quite so marked as Fig. 1. Clinically, the degree of hyperthyroidism corresponded. Lobulation well defined, small acini in periphery. Increase in stroma and parenchyma over open or colloid spaces. Lace-like appearance. Acini irregular in size and form. Blood and lymph vessels markedly dilated, some lobules almost entirely made up of epithelial elements.

their contents. The ends were convex towards the lumen of the acinus and the cell was also convex on its side margins, making it barrel-shaped; this condition, I suppose, was due to the fact that because of its activity it was full of secretion. The nuclei were set near the base of the cells and were stance contained within the cytoplasm in very minute droplets. The margins of these droplets were outlined by a very fine granular material, staining pink with eosin. The colloid-like material did not stain with eosin.

The above description relates in detail not only to the histological picture

of the three cases reported in this paper, but also to the microscopical appearance of the gland in the fifteen other cases of exophthalmic goitre in which iodine was not administered. Moreover, the microscopical description of the sections of gland removed was at once struck with the enormous increase in the fibrous connective tissue disseminated very irregularly throughout the gland. The interlobular as well as the intralobular stroma was definitely increased. There was a true *sclerosis* of the gland. By far

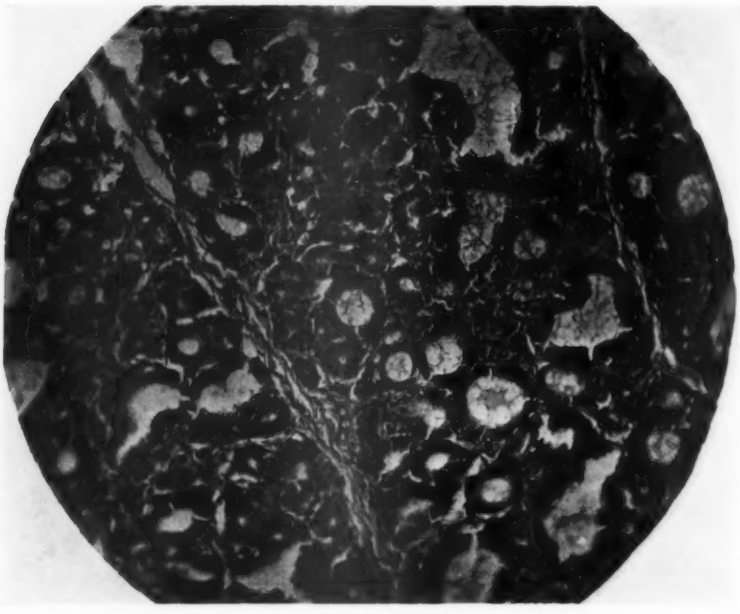

Fig. 6. High power, 4 mm. lens. Ocular 4 × —magnification, 176. Higher magnification of Fig. 5. Case 3. Stroma containing dilated lymphatics and blood vessels, very plain. Colloid highly refractile. Acini empty or containing vacuolated colloid. Epithelium elevated columnar and many papillomatous ingrowths. Stroma increased.

after the patients had been treated with iodine applies not only to the three cases included in this paper, but also to the fifteen other cases in which I operated after iodine had been given as a pre-operative treatment.

The changes in the histological picture were most marked (Fig. 7). In studying the sections of a gland removed after iodine treatment, one the most pronounced and striking change was the increase in the amount of colloid; whereas before treatment with iodine it was scant, poorly staining, or absent, after treatment it was plentiful, distended the acini, large and small, and stained uniformly throughout. Occasionally, there were areas of slight staining with eosin and even vacuolation, but this was unusual.

The acini were much more regular in size and form. Approximating more nearly the normal histological picture, the acini retained some slight irregularity, but in general suggested much more the colloid or resting state. There was still some slight infolding, voluting process. The lobules were not so plainly defined because of the marked distention of the individual acini and the increase in amount of fibrous tissue in the intra-acinar stroma. The peripheral arrangement of the small acini did, however, per-

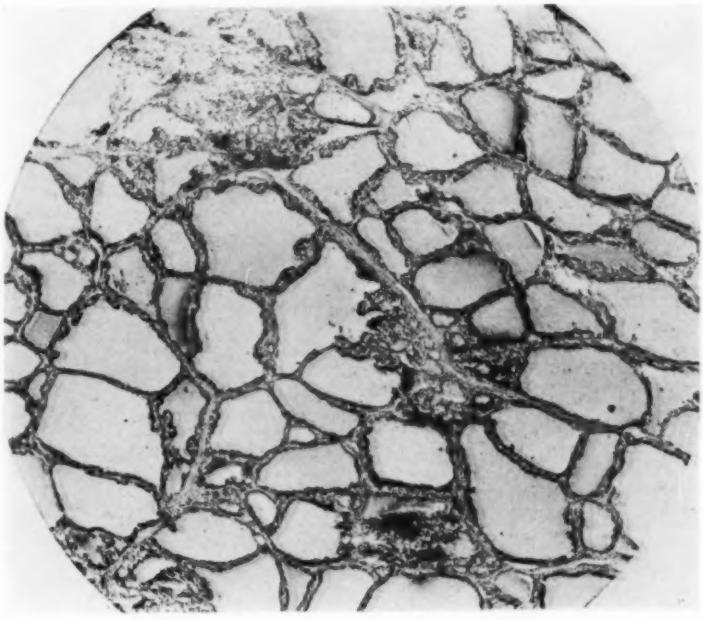

FIG. 7. Low power, 16 mm. lens. Ocular 4 × —magnification, 40. Case 1. After administration of iodine. Typical sections from right inferior, left superior and inferior polar region of thyroid gland. Striking contrast to Fig. 1, although from the same patient. Colloid-containing spaces greatly predominate over parenchymatous portion of gland. Although sections show definite approximation to colloid or resting state, there are still some sprigs and mounds of epithelium which protrude into center of acinus. In the process of flattening out from intraacinar pressure, even-staining colloid completely fills acini and epithelium abuts colloid. Stroma connective tissue increased. Certain areas with entire lobules filled with smaller acini persist. Acini more regular in form and size.

but the lace-like structure of Fig. 1 was practically obliterated, and dilated distended acini with relatively smooth walls had taken its place (Fig. 8). The occasional sprigs and mounds in the acini were evidence I think, of an in- sist in some of the lobules. The acini, in general, were much more distended with colloid than before iodine was given, the colloidal deposit or accumulation being probably a mechanical factor in distending or ballooning out

the acini. In most of the lobules the smaller acini, which were very apparent in the sections of a gland removed before iodine was used, had disappeared to a great extent; may this not have been due to the fact that they represented, as MacCallum has suggested, not only a few new or growing alveoli, but also diverticula of the large central acinus, which became uncurled or unfurled by the distention or increase in intra-acinar pressure due to the newly formed and deposited colloid? The blood vessels and lymphatics were much less evident. The fluid content of the gland seemed to have diminished, especially as regarded the blood and lymph flow. The blood vessels appeared to be collapsed by the pressure of the distended acini.

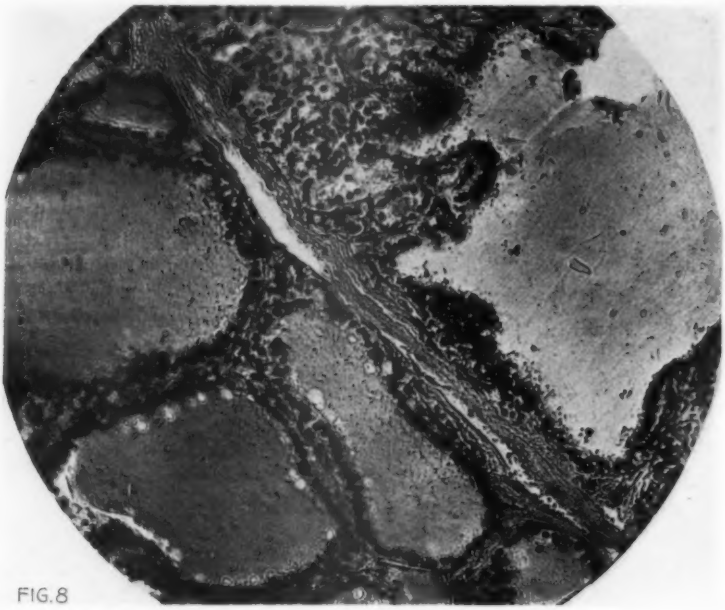

FIG. 8

FIG. 8. High power, 4 mm. lens. Ocular 4 × —magnification, 176. Case 1, after iodine. Higher magnification of Fig. 7. Colloid even-staining and markedly increased. Vessels and lymphatics in stroma compressed. Epithelium flattened, cuboidal and shrunken with pyknotic nuclei. Compare with Fig. 2, which is high power before iodine was given. These sections from same patient. Striking difference. Some infolding of epithelium in Fig. 8 shows the section still to be classed as one of exopthalmic goitre but much more mild or less active than the picture in Fig. 2. The clinical picture changed accordingly. In upper part of Fig. 8 there is shown a portion of a lobule in which the acini have persisted and resisted the involutionary changes or transformation induced by the iodine elsewhere. These areas are frequent throughout the section.

The epithelium had undergone most remarkable changes. The cells varied in size and shape. There still remained some low columnar epithelial cells which had not undergone a complete change into the resting or

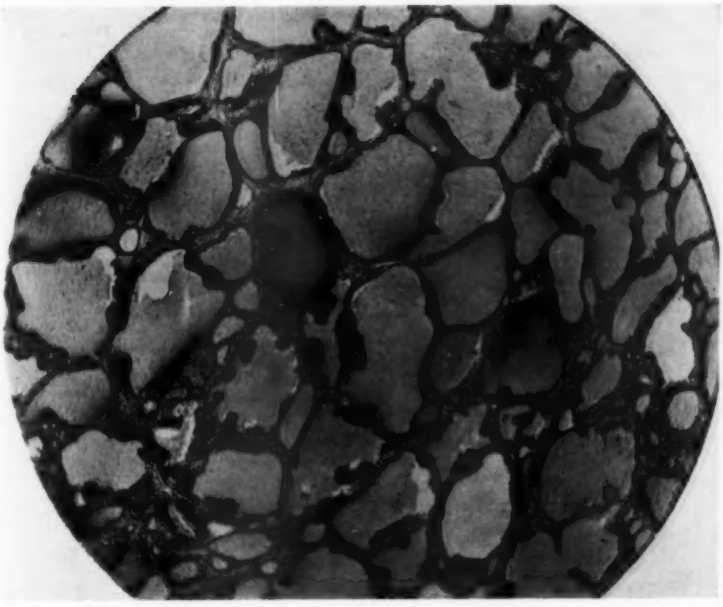

FIG. 9. For legend see Fig. 7

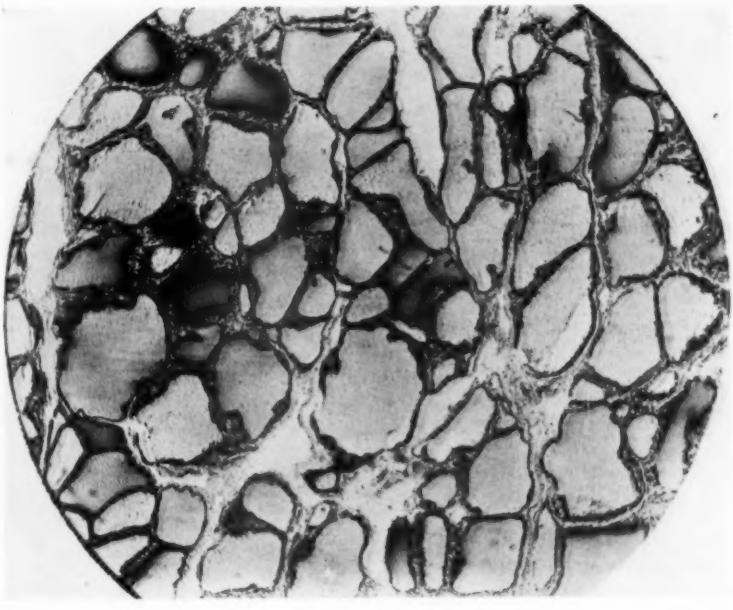

FIG. 10. For legend see Fig. 7

normal size and shape. The majority of acini were lined with flat cuboidal cells, and in some the cytoplasm was so markedly diminished that the nuclei with the cells in the gland removed before the administration of iodine, they seemed quiet, inactive, and shrunken. The ends abutting the

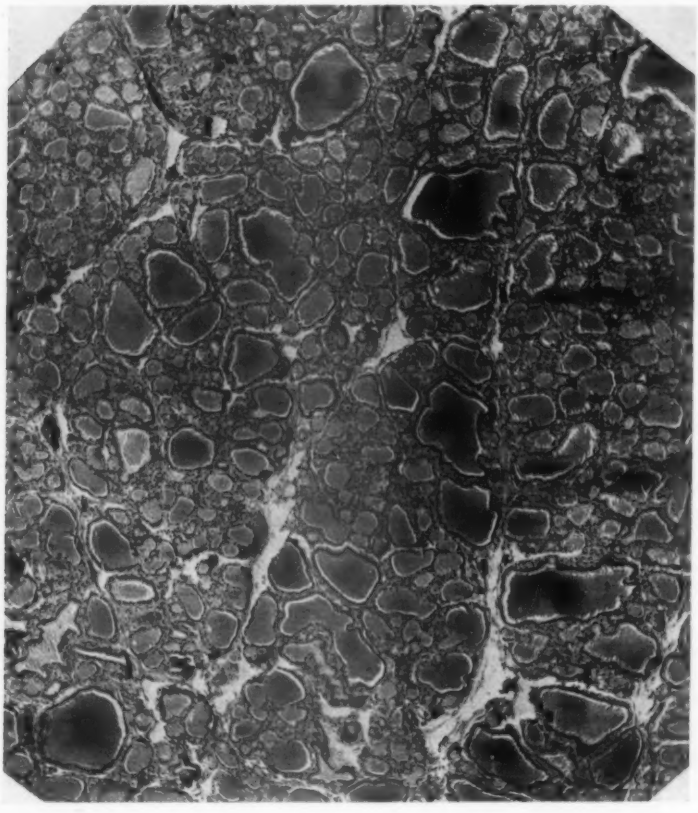

FIG. 11. High power, 16 mm. Ocular 4 × —magnification, 40. Case 2, after iodine. Superior and inferior regions of left lobe of thyroid. Inferior region of right lobe. Increase in amount of colloid at expense of parenchyma; colloid even-staining and completely filling acini. Acini more regular in size and form. Fibrous stroma increased. Even small acini are distended with colloid. General structure of the gland much less active.

stood out like pearls in a necklace. The epithelial cells, on the whole, had undergone a complete transformation, and much more nearly approximated the normal thyroid cell. As compared colloid were concave, as were also the sides of the cell, instead of being full and convex. The cytoplasm was much more finely granular, and these granules were diffusely distributed,

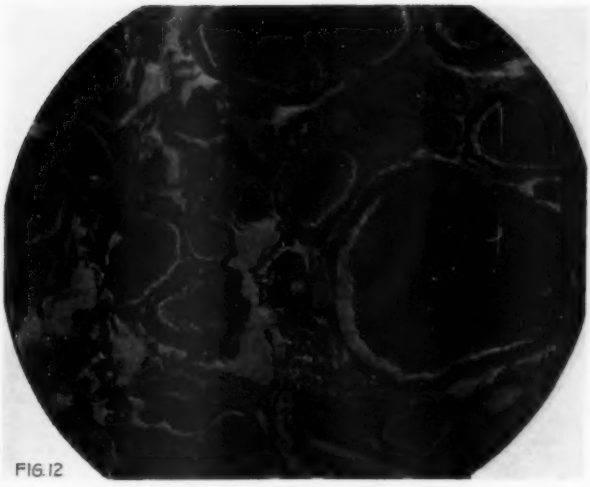

FIG. 12. High power, 4 mm. lens. Ocular 4 × —magnification, 176. Higher magnification of Fig. 11. Case 2, after iodine. Increased even-staining colloid completely filling acini. No shrinking or vacuolization. Compare colloid of Fig. 12 with that of Fig. 4, which is a high power of the right upper pole of the same case. The colloid before iodine and afterward is very different. In Fig. 12 the epithelium is uniformly flattened and cuboidal, stroma increased, vessels collapsed. Comparison of the histological details of Figs. 4 and 12 shows quite a marked change.

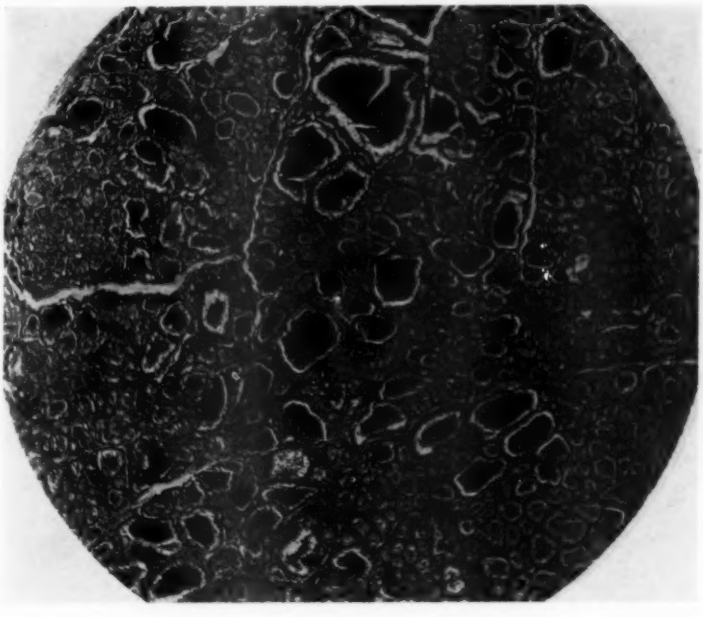

FIG. 13. For legend see Fig. 11

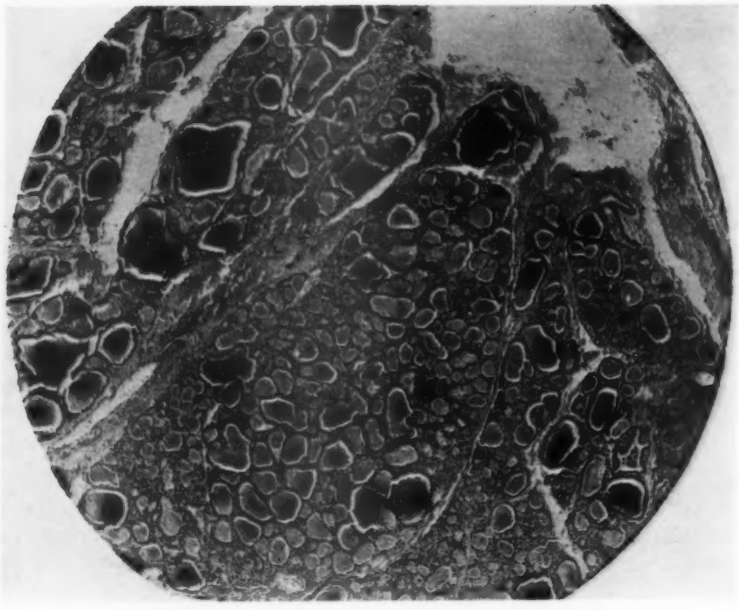

FIG. 14. For legend see Fig. 11

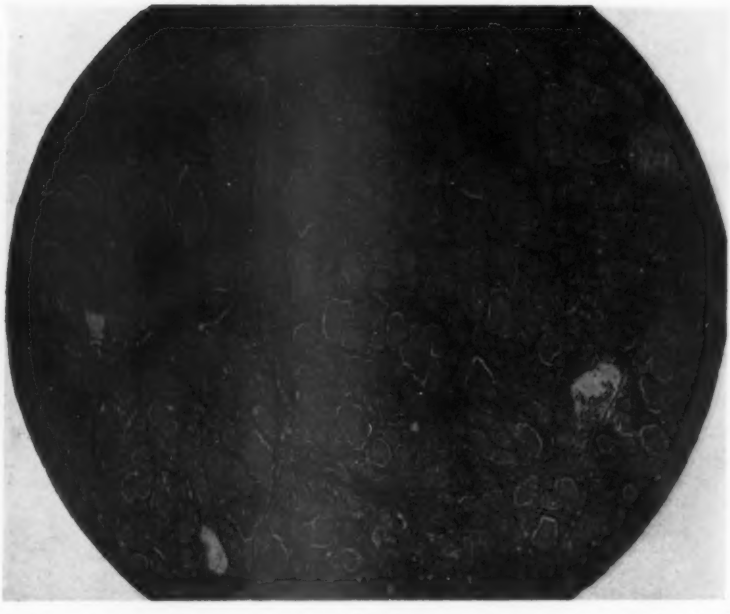

FIG. 15. Low power, 16 mm. 4 ×—magnification, 40. Case 3, after iodine. Section from left lower, upper and right lower polar regions of gland. Two chief characteristics of these sections stand out, (1) the increase and uniformity of deposition of the colloid throughout, (2) the pyknotic nuclei give the section an almost granular appearance. The scarring here is quite pronounced. The fibrous tissue of the stroma is also increased.

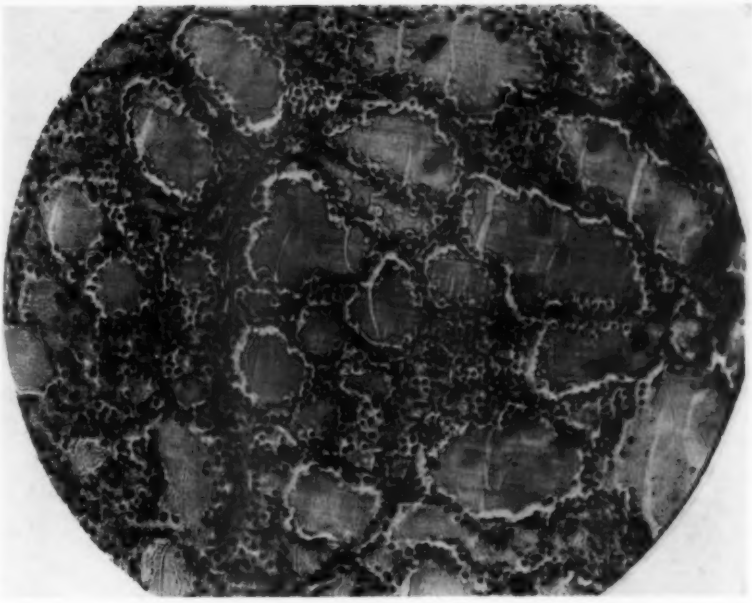

FIG. 16. High power, 4 mm. Ocular 4 × —magnification, 176. Case 3, after iodine. Higher magnification of Fig. 15. Colloid markedly increased, even-staining and not vacuolated. Compare with Fig. 6 which has the same magnification of Case 3 before iodine. Flat cuboidal epithelium with pyknotic nuclei. Epithelium seems very inactive when compared with Fig. 6. Occasional areas of groups of small acini which persist, and resist the changes usually brought about by iodine.

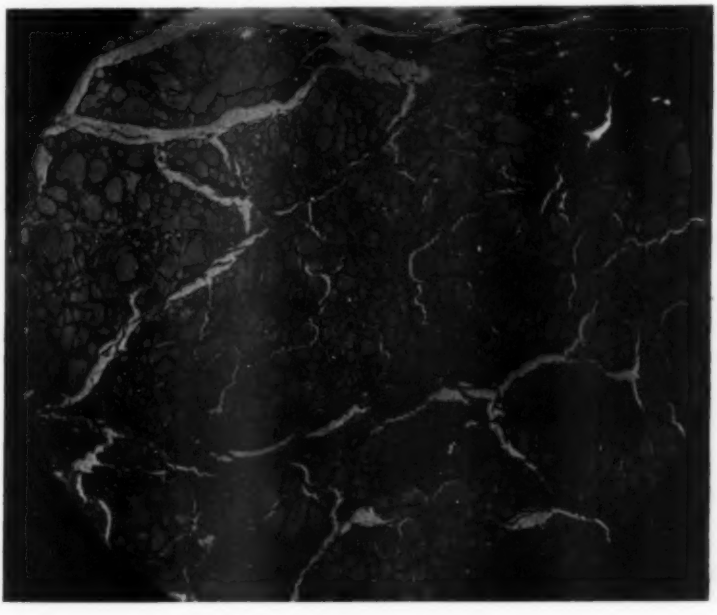

FIG. 17. For legend see Fig. 15

giving the cytoplasm of the cell a very even staining and uniform granulation. No colloid-like droplets were observed. The cytoplasm was not mottled. The nuclei seemed smaller, more pycnotic, and irregular in contour. They stained intensely with hemotoxylin. No mitotic figures could be found. No areas of solid epithelium were made out, there were only occasional sites of lymphatic infiltration, and no acini filled with desquamated epithelial cells or red blood cells.

FIG. 18. For legend see Fig. 15

SUMMARY

I have described three successive typical cases of exophthalmic goitre, in each of which the basal metabolic reaction was well above 50 and in each of which, under local anaesthesia, the right upper pole of the thyroid gland was excised, care being taken not to interrupt the continuity of the superior thyroid artery or vein on that side. The circulation to the gland was disturbed as little as possible. The tissue was handled very carefully and immediately placed in fixing solution at the operating table. The patient was then given iodine in the form of Lugol's solution, ten minims three or four times a day. In addition to a striking clinical improvement there was also a precipitous drop in the basal metabolic rate of each. The patient, clinically, more nearly approximated a normal person than before iodine was given. The gland was then removed and examined. The histological studies before and after the use of iodine revealed the fact that there had taken place during the period in which

iodine was administered striking changes in its structure. The changes most evident were: (1) an increase in the gross size and appearance of the thyroid gland; (2) decreased vascularity of the gland; (3) very marked increase in the amount of colloid present, this being evident in both gross and microscopic examinations; (4) increase in amount of fibrous tissue in the capsule and in the interlobular and intralobular stroma; (5) the presence of small tumefactions resembling beginning adenomata; (6) the presence of epithelium, flat cuboidal in general, in some areas low columnar in type. A comparison of this type of epithelium with the high columnar epithelium present before the administration of iodine was very striking, the new cells being shrunken and the nuclei pycnotic; (7) blood and lymph vessels markedly collapsed; (8) acini distended, with even staining and abundant colloid. A few sprigs and mounds of the inturned margins of the acini remained, but the papillomatous ingrowths of epithelium had been to a great extent mechanically flattened and uncurled by the increased intra-acinar pressure due to the marked increase in accumulation of colloid. Thus, the acini had become more normal in appearance, being regular in form and size, and the walls, instead of being irregular in shape, were smooth and even; (9) marked decrease in the number of mitotic figures seen; (10) almost complete absence of epithelial desquamation in the acini.

Of 30 patients upon whom I operated for exophthalmic goitre fifteen received iodine and fifteen did not. The comparison of the microscopical pictures of the thyroid gland removed from those that did not receive iodine with the pictures of those that did, corresponds almost exactly to the above study of the same gland before and after the administration of iodine. The microscopical picture of the thyroid gland in cases of exophthalmic goitre which have been subjected to the influence of iodine medication is fairly typical and constant.

DISCUSSION

In this clinic, the Mayo Clinic and in the Massachusetts General Hospital, Boston, it has been demonstrated clinically that there is a marked improvement in about 90 per cent of the patients with exophthalmic goitre who have been treated with iodine. This improvement seems to be temporary, but nevertheless is quite definite and beneficial if followed by proper surgical therapy. As a result of this study I believe it can be stated that the histological changes brought about in the thyroid gland are the result of the administration of iodine, and that these changes were produced in the other twelve cases treated in the same manner. Series of sections were made in each case from all portions of the gland removed. The histological changes were constant throughout the gland. Series of sections were made from the entire right upper pole in order to obtain a representative histological picture. The superior thyroid artery and vein were left unharmed so as to prevent any local disturbance in the gland as a result of diminution in the blood supply through these vessels. As was shown by Giordana (12) and confirmed by our observation in this clinic, there are local changes in the thyroid gland immediately adjacent to

the site of ligation of a vessel; however, this does not affect the remainder of the gland at a distance from the ligated pole. An operative procedure alone, without the use of iodine, does not influence the histological picture in the distant remaining portion of the thyroid gland, as proved by examination and comparison of the microscopical pictures of cases in which only one side of the gland was removed, to be followed by removal of the remaining gland shortly (two to four weeks) afterwards. In several cases so examined the histological pictures of the two portions of the thyroid removed at two different times were identical.

In one other case the gland showed a typical picture of exophthalmic hypertrophy which had reverted to the colloid state under the administration of iodine, the basal metabolism having fallen from +51 to +25. The patient was operated upon and discharged with a basal metabolism of +2. Seven months afterwards the patient returned, having noticed a "lump" at the site of operation. This lump proved to be a recurrence at the tracheo-esophageal angle, about the size of a green olive. The histological picture was typical of exophthalmic goitre. The basal metabolic rate had gone up to +14 from +2 on discharge following the primary operation. This, then, is a demonstration that iodine caused a reversion of the gland to a colloid or resting state, but that after this reversion there was a clinical exacerbation, the gland becoming active and presenting the histological picture of exophthalmic goitre after the influence of the iodine had passed off.

If one examined only the sections from cases in which iodine had been given, one would be forced to call them histological pictures of exophthalmic goitre, but when they are compared with sections of glands removed before iodine was given, the change from a very active hyperplasia to a resting colloid state is at once evident. Whether one cares to call the change an involution to a less active, colloid state, a remission, or a hypoplasia is a matter of choice.

I think it can be said that, associated with the clinical picture of typical exophthalmic goitre or Graves' disease, there is a definite histological picture which was first pointed out by Halsted (13) and later so well described by MacCallum (11). It is also shown that if these patients are treated with some form of iodine, there is a marked clinical improvement accompanied by a fall in the basal metabolic rate, a condition which is directly associated with a change in the histological structure of the thyroid gland, from a marked classical hyperplasia to a more colloid or less active state more nearly approximating an inactive colloid goitre or even a normal gland. After making a careful review of the literature I believe that this study presents the first properly checked evidence of the histological changes produced by the action of iodine on the thyroid gland in cases of exophthalmic goitre. It is perfectly obvious to one who has studied a series of sections of cases of exophthalmic goitre that, unless a comparison of tissue removed before and after the administration of iodine is made in each case, one cannot conclude that any changes have been brought about solely by the iodine.

It has been known for many years that in cases of exophthalmic goitre there are definite periods of remission and exacerbation, and it has been thought that the ideal time to operate upon the patient was during one of the remissions. However, the decision as to just when the exacerbation ends and the remission begins has been a difficult one to make. The varied histological pictures associated with cases of hyperthyroidism bear witness to the fact that in some patients the hyperplasia and hypertrophy is much more pronounced than in others. Until the advent of the basal metabolism test as a measure or indication of the degree of hyperthyroidism, we have had no standard by which we could decide how sick the patients really were, so that a study of the histological structure of the gland in connection with the histories furnished only very inadequate data for comparison. The personal equation as represented by the examining clinician was very difficult to standardize. In this study it has been shown, both by the three cases reported and by the twenty-seven others referred to, that the typical case of exophthalmic goitre of Graves' disease is characterized by a high basal metabolism and a histological picture of marked hypertrophy and hyperplasia, and it has been demonstrated that after administration of iodine the cases are, clinically, markedly improved, the basal metabolism drops (according to Means 3.7 points a day), and the *histological picture of the gland is changed to a resting colloid state more nearly approximating the histological picture of the normal thyroid gland.* In other words, an artificial involution, reversion, or remission to a more colloid state has been brought about during the administration of iodine. The histological picture has changed from one showing columnar cells, large vesicular clear nuclei, dilated vessels, scant colloid, papillomatous ingrowths of acini, many mitotic figures, and all the other histological criteria of glandular activity, to a picture of abundant colloid, regular dilated acini, cuboidal cells, pycnotic nuclei, increase in connective tissue, and thrombosed vessels, all of which are undoubted histological evidence of at least diminished glandular activity.

There has always been much conjecture on the part of pathologists as to whether the colloid state was not as active in a way as the hyperplastic state, and whether or not it could be properly termed a "resting state" of a hyperplastic gland. These cases demonstrate, I believe, that the iodine produces a marked clinical remission which is associated with a fall in the basal metabolism. This clinical improvement is accompanied by the reversion of the hyperplastic thyroid gland to the colloid or resting state, and clinically as well as histologically this state is less active than the hyperplastic and hypertrophic stage. In going over a series of five hundred microscopical slides of patients with exophthalmic goitre operated upon and autopsied in this clinic in the last twenty-five years, I have found all gradations of the histological picture associated with a clinical syndrome which is correspondingly mild when the colloid or resting state is present and severe when the hyperplastic state is found. *The clinical picture varies directly with the histologi-*

cal structure. The conclusion seems justifiable that the colloid or resting state is histologically and clinically less active than the hyperplastic state. How iodine brings about an artificial or immediate remission I do not know, but that it does I am certain, and the objective changes in the histological structure of the thyroid gland as a result of the administration of iodine are those above described.

Because of the fact that exophthalmic goitre does not occur spontaneously in animals and in all its phases has not been produced experimentally, it is not to be wondered that a standard histological picture has not been described. The clinical picture of cases, in regard to their severity, is subject to the widest and most varied interpretation depending on the individual examining the patient and also on the stage of the disease at the time of examination. In our cases we have in the beginning a picture of marked exophthalmic goitre, both clinically and histologically, and as the clinical picture approximates normal following the ingestion of iodine, the transition is accompanied by the histological changes described above. In one case shown there was a recurrence after an artificial remission had been brought about by iodine. In this case an exophthalmic type, a hyperplastic condition, was observed to change to a colloid or resting state, with an amelioration of signs and symptoms and a fall in the basal metabolic rate; following this the symptoms recurred, the basal metabolism rose, and the histological picture reverted from the colloid or resting state to a hyperplastic condition, or a typical picture of exophthalmic goitre.

These facts would seem to indicate that clinically typical Graves' disease or exophthalmic goitre is accompanied by a classical microscopical picture of hypertrophy and hyperplasia of the thyroid gland. That these cases undergo remissions and exacerbations is a well known clinical fact. That an artificial remission by iodine is produced and is accompanied by changes from a hyperplastic to a colloid state, I have shown in this study. The varied histological picture observed in any long series of cases of exophthalmic goitre is determined, it seems to me, by the stage of hypertrophy and hyperplasia of the gland. Whether or not the gland is entering on an exacerbation or a remission depends on the clinical history and examination. One of the most important facts to be gained from this study is, I think, that there is a standard histological picture for exophthalmic goitre and that the milder clinical modifications are associated with a reversion to the colloid state. There may be any number of clinical pictures of hyperthyroidism from the mildest to outspoken Graves' disease, and these various clinical gradations are associated with a histological picture that changes from a normal gland or resting colloid state to the most marked glandular hyperplasia and hypertrophy seen in severe cases of exophthalmic goitre, similar to the microscopical pictures described for the three cases detailed in this paper (Figs. 1 to 6).

CONCLUSIONS

1. Iodine produces definite and striking changes in the histological structure of the thyroid gland in cases of exophthalmic goitre.

2. These changes are as follows: (*a*) increase in size of the thyroid gland as a whole; (*b*) decrease in vascularity and probably in the lymph flow through the gland; (*c*) a large increase in amount of fibrous connective tissue; (*d*) a striking increase in amount of colloid deposited and contained within the thyroid gland; (*e*) a change in the acini from lace-like papillomatous ingrowths to round, even-walled smooth acini, regular in size and form; (*f*) a transition of epithelium from high columnar to flat cuboidal and occasionally low columnar; (*g*) a change in the nuclei of epithelial cells from large clear nuclei to the small irregular pycnotic type; (*h*) the presence of many mitotic figures before the use of iodine and their absence after iodine has been given.

3. The clinical improvement and the lowered rate of basal metabolism are directly associated with the change from a typical histological picture of exophthalmic goitre to a resting colloid state.

4. In comparing the histological structure of the thyroid gland in 30 cases of exophthalmic goitre, fifteen in which iodine had been given and fifteen in which no medication whatsoever had been used, it was observed that the histological picture following the administration of iodine was constant and, compared with the microscopical structure of the glands of the cases not receiving iodine, corresponded exactly, as had the microscopical changes in the three cases in which an examination of the gland was made in each patient before and after the administration of iodine.

5. The colloid state is proved clinically and histologically to be less active than the hypertrophic and hyperplastic state.

6. An artificial remission is produced by iodine.

7. A remission in a case of exophthalmic goitre is associated with a change in the histological picture from a hyperplastic to a colloid state, even though there is definite evidence of hyperplasia yet remaining. It is a question of a relative hyperplasia. This observation tends, I think, to clarify the confusing histological pictures seen in a long series of cases of exophthalmic goitre.

I wish to thank Dr. J. M. T. Finney for his very kind permission to study and report these cases. I also wish to thank Miss Carolyn Breese for her assistance in the histological preparations.

REFERENCES

(1) Coindet: Découverte d'un nouveau remède contre le goître. *Ann. de chim. et phys.*, 1920, xv, 49–59.

(2) Chatin, A.: *Compt. rend. Soc. de biol.*, 1850, xxx, 352. (Reference in Fraser.)

(3) Trousseau: Lectures on clinical medicine, London, 1868, vol. i, p. 587.

(4) Baumann, E.: Der Iodgehalt der Schilddrüsen von Menschen und Thieren. *Ztschr. f. physiol. Chem.*, 1896, xxii, 1–17.

(5) Oswald, Ad.: Ueber den Jodgehalt der Schilddrüsen. *Ibid.*, 1897, xxiii, 265–310.

(6) Roos, E.: Untersuchungen über die Schilddrüse. *Ibid.*, 1899, xxviii, 40–59.

(7) Marine, D., and Williams, W. W.: The relation of iodin to the structure of the thyroid gland. *Arch. Int. Med.*, 1908, i, 349–384.

Marine, D., and Lenhart, C. H.: Re-

lation of iodin to the structure of human thyroids. *Ibid.*, 1909, iv, 440–493.

MARINE, D.: The importance of our knowledge of thyroid physiology in the control of thyroid diseases. *Ibid.*, 1923, xxxii, 811–827.

(8) PLUMMER, H. S., AND BOOTHBY, W. N.: The value of iodin in exophthalmic goitre. *J. Iowa State M. Soc.*, 1924, xiv, 66–73.

(9) STARR, P., WALCOTT, H. P., AND MEANS, J. H.: The effect of iodin in exophthalmic goitre. *Arch. Int. Med.*, 1924, xxxiv, 354–364.

(10) FRASER, F. R.: Iodine in exophthalmic goitre. *Brit. M. J.*, Jan. 3, 1925, 1–4.

(11) MACCALLUM, W. G.: The pathology of exophthalmic goitre. *Jour. Am. Med. Assn.*, 1907, **49**: 1158–1162.

(12) GIORDANA, A. S., AND CAYLOR, H. D: Histological study of the effect of ligation of the thyroid vessels in exophthalmic goitre. *Surg., Gyn. and Obst.*, 1923, xxxvi, 75–80.

(13) HALSTED, W. S.: An experimental study of the thyroid gland in dogs, with especial consideration of hypertrophy of this gland. *Johns Hopkins Hosp. Rep.*, 1896, i, 373–408.

Reprinted from the BULLETIN OF THE JOHNS HOPKINS HOSPITAL
Vol. XXXVII, No. 5, pp. 307-327, November, 1925

Studies on the Biology of the Streptococcus erysipelatis

III. Experimental Production of Erysipelas in Rabbits and Demonstration of Protective Power of Immune Erysipelas Sera[1]

BY KONRAD E. BIRKHAUG

From the Biological Division of the Medical Clinic, The Johns Hopkins Hospital, Baltimore, Maryland

INTRODUCTION

THE conception of erysipelas as a disease associated with Streptococcus hemolyticus has been widely accepted since Fehleisen (1) in 1883 demonstrated that erysipelatous lesions could be produced experimentally in the skin of laboratory animals by intradermal inoculation of hemolytic streptococci isolated from cases of erysipelas. This finding was corroborated by Roger (2), Grammakowsky (3), a few years later by Denys and Leclef (4), Gay and Rhodes (5), Besredka (6), and more recently by Rivers and Tillett (7). All these investigators agreed that the lesions produced in the skin of animals by intracutaneous inoculation of hemolytic streptococci were not unlike the lesions observed in human cases of erysipelas. In the voluminous literature which has accumulated on the subject of experimental erysipelas with Streptococcus hemolyticus, past investigators have made numerous attempts to establish the etiology of the hemolytic streptococci isolated from erysipelatous lesions, by means of cultural and morphological studies. These methods offered no adequate criteria by which a differential diagnosis could be made between strains of erysipelas and non-erysipelas hemolytic streptococci. In a previous report (8), a biological relationship was shown to exist between individual strains of Streptococcus hemolyticus isolated from erysipelatous lesions by means of the immune reactions of specific agglutination and absorption. It was found that 91.2 per cent of the strains of streptococci isolated from typical erysipelatous lesions of erysipelas fell immunologically into one group, and this group of streptococci could be clearly differentiated from the group of streptococci associated with scarlet fever, as well as from those found in other pyogenic infections. There has been much debate about the reliability of such immune reactions as agglutina-

[1] Read before The Johns Hopkins Medical Society, February 2, 1925. Received for publication, May 7, 1925.

tion and absorption in determining type specificity among the large family of Streptococcus hemolyticus. In view of the obstacles encountered in obtaining uniform suspensions of streptococci and of overcoming the tendency of all types of streptococci to undergo spontaneous granulation, a method has been developed to determine antigenic relationships of strains of erysipelatous hemolytic streptococci by *in vivo* protection experiments. The method consisted in determining the protective power of immune sera, administered intradermally or intravenously in laboratory animals, against the injurious action of hemolytic streptococci isolated from erysipelas and non-erysipelas sources. It was demonstrated by this method that the type specificity of different strains of hemolytic streptococci corroborated the findings obtained by the *in vitro* methods alone, and thus the results obtained by these two method supplemented one another and added further value to the interpretation of existing serological relationships of one strain to another.

MATERIAL AND METHOD

The strains of Streptococcus hemolyticus employed for the production of experimental erysipelas and the preparation of immune erysipelatous sera have been described in a previous report (8). Bacterial suspensions used for the intradermal inoculations were made from 24-hour blood-agar slant cultures, which were washed off with 10 cc. of Locke's solution. The bacterial emulsions were shaken vigorously with glass-beads, and various dilutions of desired proportions of inoculum and Locke's solution were made. The rabbit's chest and abdomen were depilated on both sides of the body until the shaved area measured about 8 by 12 cm. Injections of the bacterial emulsions were made with a Luer tuberculin-syringe and a 27-gauge needle. A constant dose of 0.1 cc. of each dilution was injected intradermally.

It was found that marked variations existed among the average stock rabbits in their response to the injurious action of the inoculated bacteria. For the sake of accuracy in determining the pathogenic virulence of certain strains of hemolytic streptococci, therefore, a complete series of tests was carried out in the same susceptible animal. This procedure necessitated as many as 12 to 16 intradermal inoculations in one animal at one time. Inoculation into freshly shaved areas was avoided, since it was repeatedly observed that the irritated or abraded skin surfaces yielded results that could not readily be interpreted when compared with lesions produced in the healthy skin. In numerous instances animals succumbed to non-lethal doses of streptococci when inoculations were made into chemically or mechanically irritated skin surfaces. Twelve normal rabbits, whose blood sera were free from natural agglutinins for the streptococci used in these experiments, were employed for the study of cutaneous lesions. The results of these inoculations are shown in Table I. The rapidity with which the inflammatory reactions were demonstrable in the inoculated skin was in direct proportion to the strength of the bacterial dilutions.

NATURE OF CUTANEOUS LESIONS

Three types of cutaneous lesions were readily distinguishable following intradermal and subcutaneous injections of Streptococcus erysipelatis: (A) erythematous, (B) diffuse, and (C) phlegmonous erysipelatous lesions.

A. Erythematous lesion

Inflammation of the skin area about the site of the intradermal inoculation inoculated, the inflammatory area measured about 2.5 cm. in diameter as early as twelve hours after the inoculation. Twenty-four hours after the injection of the bacterial inoculum in dilutions as high as 1 to 500, the skin lesions became distinct in outline. The erythematous lesions were deep red in the center and the advancing margins were definitely raised and sharply delimited from the surrounding healthy tissue. The inflammatory

TABLE I

Cutaneous lesions in rabbits inoculated intradermally with streptococcus erysipelatis

RABBIT NUMBER	STRAIN OF STREPTOCOCCUS ERYSIPELATIS	DILUTIONS OF CULTURE: Ten areas were inoculated with 0.1 cc. each of virulent streptococcus erysipelatis. 0	1:25	1:100	1:200	1:300	1:400	1:500	1:1000	1:2000	HEAT-KILLED STREPTOCOCCUS ERYSIPELATIS
345	A_1	++++	+++	++	++	+	+	0	0	0	0
346	A_1	++++	+++	+++	++	+	+	0	0	0	0
347	B_3	++++	++++	+++	+++	++	+	+	0	0	0
348	B_3	++++	++++	+++	++	++	+	+	±	0	0
349	C_1	+++	+++	++	++	+	+	±	0	0	0
350	C_1	+++	+++	+++	++	++	+	+	0	0	0
351	C_4	++++	++++	++++	+++	+++	++	++	+	0	0
352	C_4	++++	++++	++++	+++	++	++	++	+	0	0
353	C_7	+++	+++	+++	++	++	+	0	0	0	0
362	C_7	+++	+++	++	++	+	+	±	0	0	0
364	C_9	++++	++++	+++	++	++	+	+	0	0	0
368	C_9	++++	++++	+++	++	++	+	±	0	0	0

The reading of the cutaneous lesions was made 24 hours after inoculation. ++++ indicates that lesion measures 4 cm. in diameter or over, +++, 3 cm., ++ and +, 2 cm. and 1 cm., respectively, ±, faint erythema at the site of inoculation, and the letter 0 indicates that no inflammatory reaction occurred.

of 0.1 cc. of hemolytic streptococci isolated from cases of erysipelas was noticeable about 12 hours after the injection. The skin was flushed to a bright red color in the center of the developing lesion. The margin of the injected area appeared slightly raised and edematous. When lower dilutions of hemolytic streptococci were reactions reached their maximal size about 60 hours after the initial inoculation with the streptococcic emulsion. Later the lesions remained discreet in outline and disappeared rapidly without becoming necrotic. Desquamation followed in all the previously inflamed areas, leaving the involved skin surfaces slightly pigmented. The

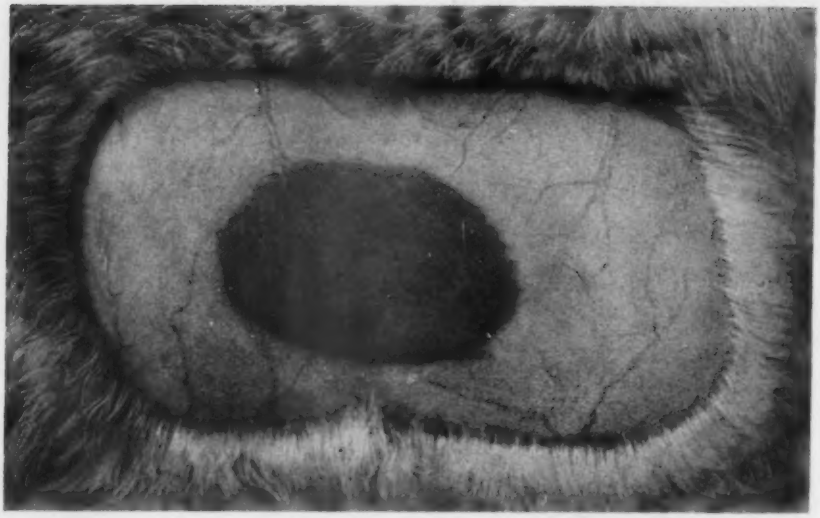

FIG. 1. ERYTHEMATOUS LESION, 24 HOURS AFTER INTRADERMAL INOCULATION OF 0.2 CC. EMULSION OF STREPTOCOCCUS ERYSIPELATIS

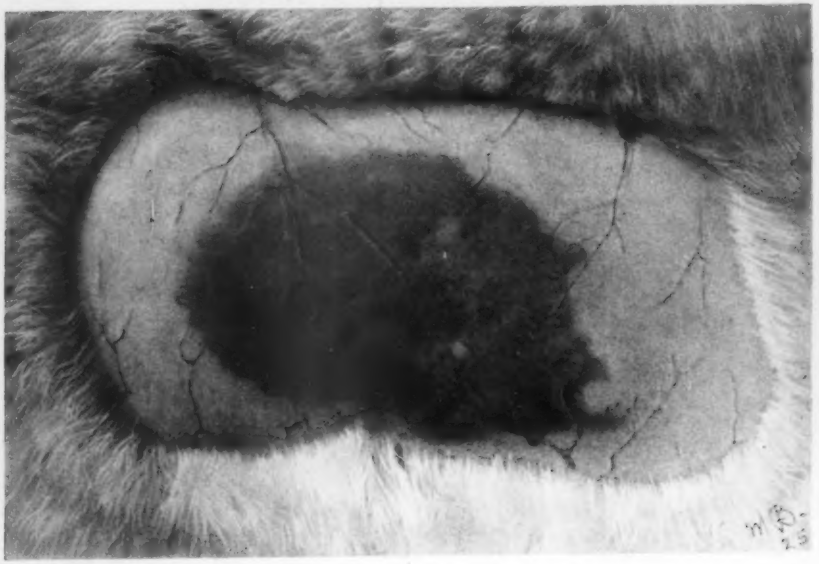

FIG. 2. SAME AS FIG. 1, 48 HOURS AFTER BACTERIAL INOCULATION

FIG. 3. PHLEGMONOUS LESION, 96 HOURS AFTER INTRADERMAL (?) INOCULATION OF 0.2 CC. EMULSION OF STREPTOCOCCUS ERYSIPELATIS

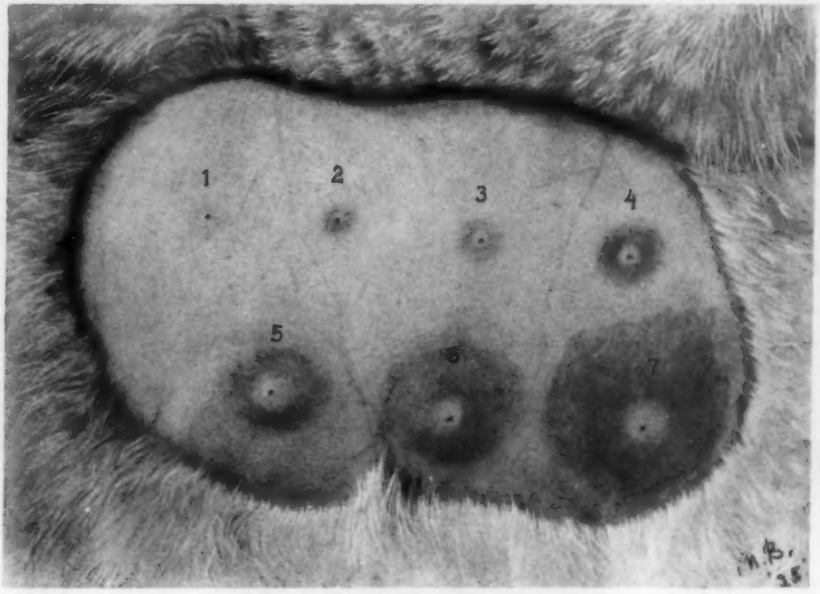

FIG. 4. LOCAL PASSIVE IMMUNITY

Intradermal infiltrations of anti-erysipelas serum as follows: (1) 0.5 cc., (2) 0.1 cc., (3) 0.05 cc., (4) 0.01 cc., (5) 0.005 cc., (6) 0.001 cc., and in (7) no serum. Twenty-four hours after serum infiltration, injected 0.1 cc. emulsion of *Streptococcus erysipelatis* in the center of each area. Inflammatory reactions observed 18 hours after bacterial inoculation.

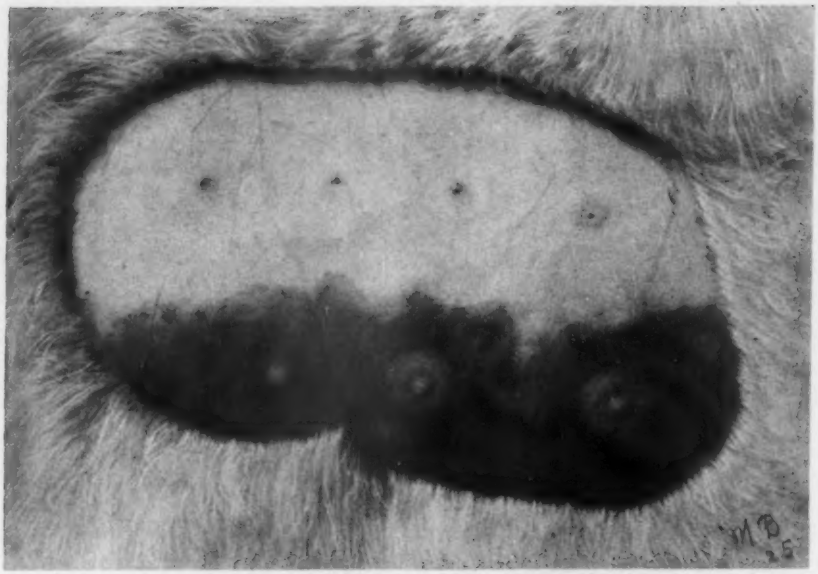

FIG. 5. SAME AS FIG. 4, 48 HOURS AFTER BACTERIAL INOCULATION

Note complete protection in areas 1–4 and the typical and diffuse erysipelatous lesions in remaining areas.

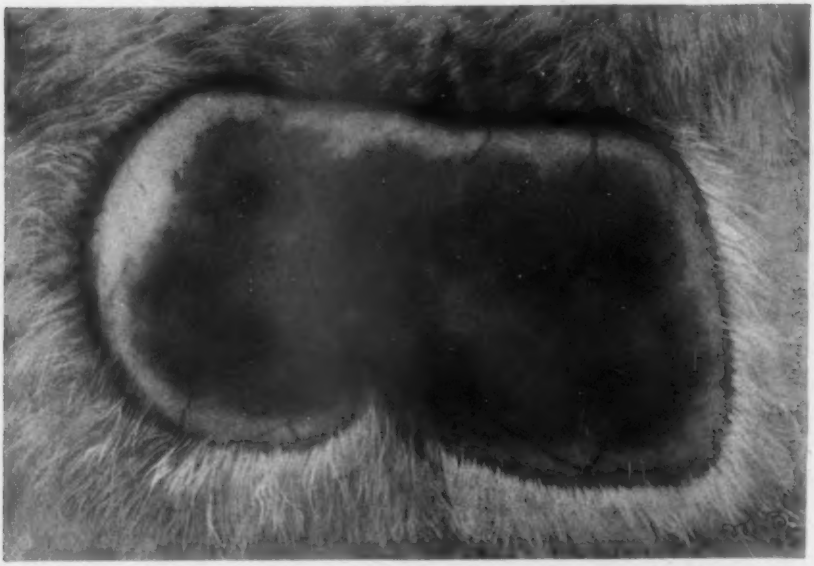

FIG. 6. CONTROL TO FIGS. 4–5

Normal rabbit serum infiltrated intradermally in same doses as in Fig. 4. Twenty-four hours after serum infiltration, injected 0.1 cc. emulsion of *Streptococcus erysipelatis* in the center of each area. Animal died 15 hours after bacterial inoculation, when drawing was made.

largest lesion following a single intradermal dose of streptococci was 6.3 cm. in diameter when observed 24 hours after inoculation, and 10.4 cm. when seen 64 hours after the injection of the streptococci. The average skin lesion which developed 24 hours after the intradermal inoculation with 0.1 cc. of undiluted streptococcic inoculum measured about 4 cm. in diameter. No definite inflammatory reaction occurred with bacterial dilutions higher than 1 to 500, except in rare instances, when lesions were observed with dilutions of 1 to 1000 of strain "C_4" (Table I).

Pathological anatomy. Sections were made of the erythematous cutaneous lesions at the height of inflammatory involvement. The pathological processes extended into the deeper layers of the connective tissue spaces. The surface epithelium was practically destroyed. A narrow zone of hyalinized material had replaced the epithelial lining. The hair-follicles, sebaceous glands and blood-vessels were surrounded by large numbers of large and small mononuclear wandering cells. Very few polymorphonuclear cells were observed. The deeper layers of the connective-tissue spaces were filled with a serous exudate, rich in fibrin, filled with mononuclear wandering cells and hyalinized connective-tissue fibers. The sections stained for bacteria demonstrated widespread distribution of streptococci, particularly numerous in the deeper layers of connective tissue corresponding to the sharply raised edge of the cutaneous lesion. The lymphatic vessels showed many streptococci, single or in chains consisting of from 4 to 10 organisms. The blood-vessels were remarkably free from streptococci (Figs. 1 to 6).

B. Diffuse lesion

The diffuse erysipelatous lesions were similar in nature to the erythematous lesions, described above, during the first 24 hours after bacterial inoculation. Forty-eight hours after the injection of 0.1 cc. of the bacterial inoculum the rapidly advancing inflammatory areas of each injected area merged into one another until they formed a large, dense and edematous area, uniformly red throughout the involved surfaces. The spread of the lesion extended rapidly beyond the shaven hair-line, and the sharply defined border of the lesion gradually disappeared into the adjoining skin. The central portion of the lesion became purplish-pink in color; the animal appeared prostrated; diarrhea developed and hematuria and hemoglobinuria were present shortly before the death of the animals (Fig. 6).

Pathological anatomy. Sections of the diffuse cutaneous lesions presented the same pathological changes that were seen in the erythematous lesions, except that a conspicuous absence of leucocytes was noted in the involved areas. The distribution of streptococci had extended to the blood-vessels in which were seen numerous bacteria.

c. Phlegmonous lesion

The phlegmonous lesions occurred in animals inoculated subcutaneously by accident, as well as after intradermal inoculation with heavier suspensions of streptococci. In several instances combinations of the erythematous and the phelgmonous lesions appeared in the same animal, in close proximity

one to the other, when apparently similar doses of bacterial inoculum were injected with identical technique. The phlegmonous lesions at first resembled the erythematous and diffuse cutaneous lesions for as long as 24 hours after the bacterial inoculation. At this time the central portion of the inflamed and edematous areas appeared distinctly pale and slightly yellow in color. The margins of these lesions were deep red and remarkably regular in outline. The following day the central portion of the lesions became very tense and unusually white in color. At this time the phlegmonous process bulged forward and the central tumefaction was much greater than that observed in the erythematous and diffuse lesions. The central swelling increased rapidly in size and projected as much as 1 to 2 cm. above the healthy skin surface. Sloughing and central necrosis occurred during the first week after the inoculation of bacteria. Underneath the scab was seen a thick, whitish pus, which continued to be discharged freely for many weeks following the rupture of the phlegmon. The culture of this pus yielded a scanty mixture of streptococci and staphylococci. The smaller phlegmons were found to persist for only a few weeks and were absorbed without becoming necrotic. After complete absorption small calcified nodules remained at the sites of the phlegmonous processes (Fig. 3).

FIG. 7. GENERAL PASSIVE IMMUNITY

Intravenous injection of 5 cc. anti-erysipelas serum. Twenty-four hours later, injected intradermally 0.2 cc. emulsion of *Streptococcus erysipelatis* (upper left) and 0.2 cc. undiluted 96-hours toxic filtrate of *Streptococcus erysipelatis* (lower right). Drawing made 24 hours later. No subsequent lesions.

Pathological anatomy. Sections of the phlegmonous processes differed little from the pathological picture of streptococcic and staphylococcic abscesses. Streptococci were seen in the upper layers of the skin only; the lymphatic vessels were notably free from any bacteria.

The mechanism underlying the production of phlegmonous lesions following intradermal inoculation of hemolytic streptococci was carefully studied in animals in whom the streptococci likewise produced the erythematous, erysipelas-like lesions. It was observed that chemical or mechanical irritation of the skin surfaces previous to inoculation of bacteria rarely predisposed to the development of phlegmons. On the other hand, when bacterial suspensions were injected intradermally in excess of 0.1 cc., in the heavier concentrations of streptococci, it was found that phlegmons invariably developed at the site of inoculation. When similar injections were made subcutaneously, phlegmonous lesions usually resulted. The coexistence side by side in the same animal of erythematous and phlegmonous processes in response to identical inoculations of the same bacteria strongly contradicts the hypothesis that local immunity against the injected streptococci plays a rôle in the development of phlegmons. That the lysis of the streptococci can be attributed to phagocytosis or to the action of ferments originating in the cells of the injected area, as was suggested by Turro and Domingo (14) in their work on local immunity and the lysis of the typhoid bacillus, must necessarily be discarded in our studies, since the erythematous erysipelas-like lesion developing in close proximity to the phlegmonous process should likewise have yielded to the inhibiting action of lysins or ferments present in the skin. A more satisfactory explanation of the development of phlegmonous lesions must be advanced. It is not difficult to suppose that some of the bacterial inoculum was forced into the subcutaneous tissue by the increased intradermal tension created by the injection of large amounts of streptococci intradermally. On the other hand, the frequency with which staphylococci were found in mixed culture with streptococci in the pus aspirated from the phlegmonous lesions, suggested that a superimposed pus-forming pathogen was introduced, either dragged down with the needle from the skin surface at the time of inoculation, or admitted through the fresh wound produced by the needle-puncture.

PRODUCTION OF ANTI-ERYSIPELAS SERUM

Three methods of inoculation were employed for the production of immune serum: (*a*) intravenous, (*b*) intracutaneous, and (*c*) intracutaneous in previously injected agar. The preparation of seven immune erysipelas sera by these three methods has been fully described in a previous report (8). The highest and most durable agglutinin titer was obtained by Dochez' method of intracutaneous injection of melted agar into which live streptococci were inoculated. Inactivation of the immune sera at 56°C. was found to accelerate the deterioration of the agglutinins in the anti-erysipelas sera. In the following experiments, therefore, freshly prepared,

unheated sera were always employed in order to obtain the highest possible protection with both homologous and heterologous strains of Streptococcus hemolyticus. For control purposes, normal rabbit serum or immune erysipelas serum, heated for half an hour at 60°C., was employed.

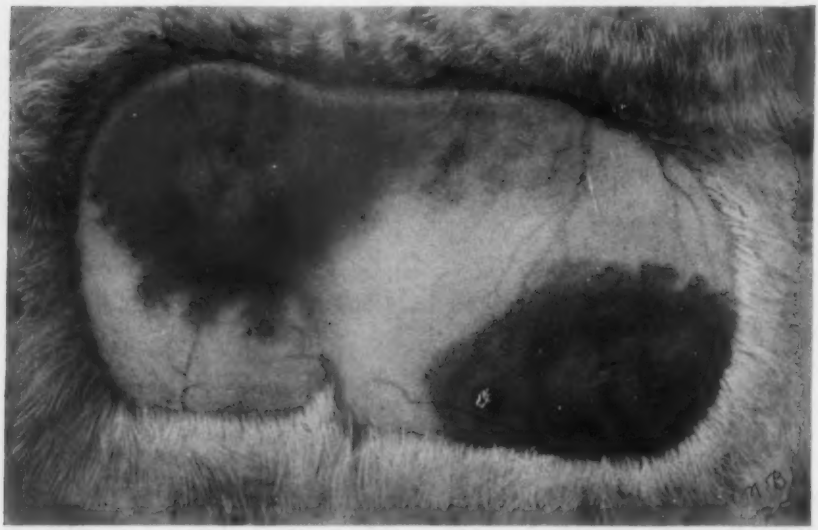

FIG. 8. CONTROL TO FIG. 7

No intravenous administration of anti-erysipelas serum. Lesions developing 48 hours after intradermal inoculation of 0.2 cc. emulsion of *Streptococcus erysipelatis* (upper left) and 0.2 cc. undiluted 96-hour toxic filtrate of *Streptococcus erysipelatis*.

INTRADERMAL PROTECTIVE POWER OF IMMUNE ERYSIPELAS SERA

Twelve rabbits whose blood-serum contained no natural agglutinins for the hemolytic streptococci employed in the protection experiments were selected to determine the presence in the immune erysipelas serum of any protective power against the injurious action of hemolytic streptococci when the immune serum and the streptococcic inoculum were injected intradermally. Since it was previously observed that there existed in the skin of laboratory animals marked differences in susceptibility to the injurious activity of hemolytic streptococci, it was found necessary to discard as useless the ordinary routine laboratory practice of running control animals in order to insure definite interpretation of skin reactions. Conflicting results so often encountered in our early experimentation from the use of the old criterion of employing other animals for the purpose of control were overcome by performing the experiment on one side and the control on the other side of the body of the same animal. The technique employed in these experiments was as

follows: The rabbit's chest and abdomen were depilated on both sides of the body, which left an area of shaved skin that measured about 8 by 12 cm. on either side of the body. The mixture of immune erysipelas serum and hemolytic streptococci was made in definite dilutions in 6 test-tubes. The diluent employed was Locke's solution and the amount of immune serum contained in the series of 6 test-tubes was as follows: (1) 0.5 cc., (2) 0.1 cc., (3) 0.05 cc., (4) 0.01 cc., (5) 0.005 cc., and (6) 0.001 cc. To each test-tube containing immune serum was added 0.5 cc. of a bacterial emulsion of hemolytic streptococci prepared from a blood-agar slant growth mixed with 10 cc. of Locke's solution. The mixture of immune serum and streptococci was incubated for one hour at 37°C., being shaken every ten minutes to insure a uniform combination of antigen and antibody, a method suggested by Neisser and Lubowski (9). For control purpose, a similar series of test-tubes were set up in which normal rabbit serum or immune erysipelas serum, heated for 30 minutes at 60°C., were substituted for the unheated immune erysipelas serum. These controls were likewise incubated for one hour at 37°C. and shaken every ten minutes during incubation.

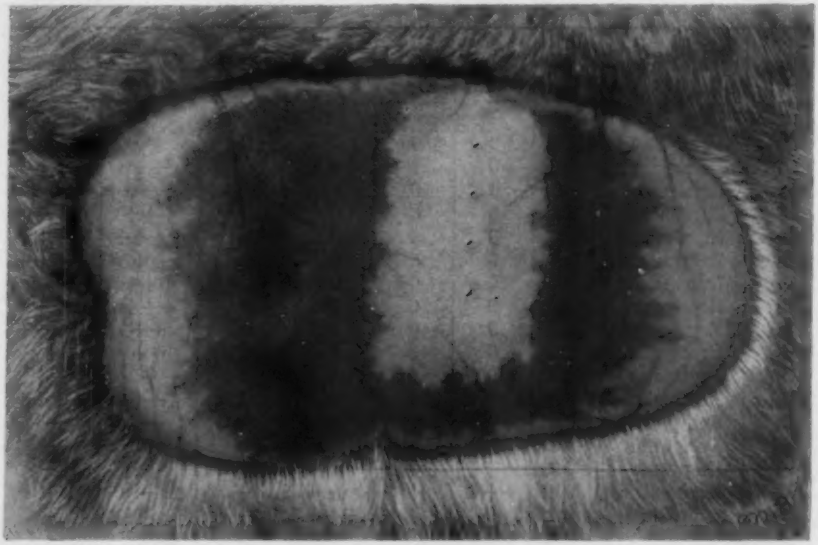

FIG. 9. REFRACTORY ZONE

Intradermal infiltrations of 0.1 cc. anti-erysipelas serum in each of 4 places (central row). Twenty-four hours later intradermal inoculations of 0.1 cc. emulsion of *Streptococcus erysipelatis* in the center of the areas infiltrated with anti-erysipelas serum and in two rows on either side of the passively immunized zone. Drawing made 24 hours after bacterial inoculation.

Intradermal inoculations of 0.1 cc.

of each dilution of immune serum and streptococci were made on the one side of the body by means of a Luer tuberculin syringe and a 27-gauge needle. The injections of the six different mixtures of immune serum and streptococci were made in two rows, about 4 cm. from one another On the other side of the body control injections were made with the six mixtures of normal rabbit serum or heated immune serum and streptococcic emulsions.

Twenty-four hours after the injections, it was observed (Table II) that 0.01 cc. of immune erysipelas serum afforded complete protection against the injurious action of 0.1 cc. of the virulent homologous culture of erysipelatous streptococcus. Only a slight redness and sharply localized swelling, measuring about 0.7 cm. in diameter, was seen in the area inoculated with 0.005 cc. of "B_3" immune serum and 0.1 cc. of the homologous culture. In dilutions of immune erysipelas serum higher than 0.005 cc. and mixed with 0.1 cc. of streptococcic

TABLE II

Intradermal protective power of immune erysipelas serum "B_3" against strains of the homologous and heterologous types, and for non-erysipelatous strains

STRAINS	TYPE OF STRAINS	DOSE OF CULTURE IN	DOSE OF SERUM					
			0.5 cc.	0.1 cc.	0.05 cc.	0.01 cc.	0.005 cc.	0.001 cc.
		cc.						
B_3	Erysipelas	0.1	0	0	0	0	±	+++
B_3	Erysipelas	0.2	0	0	0	0	++	++++
B_3	Erysipelas	0.5	0	0	++++	+++++	+++++	+++++
C_1	Erysipelas	0.1	0	0	0	0	+++	++++
C_1	Erysipelas	0.2	0	0	0	++	++++	++++
C_3	Erysipelas	0.1	0	0	0	0	++	++++
C_4	Erysipelas	0.1	0	0	0	++	+++	+++++
C_7	Erysipelas	0.1	0	0	0	0	+++	++++
C_{10}	Erysipelas	0.1	0	0	0	0	++	++++
C_{14}	Erysipelas	0.1	0	0	0	0	++	+++
C_{21}	Erysipelas	0.1	0	0	0	0	+	++
C_{24}	Erysipelas	0.1	0	0	0	0	++	++++
D_1	Cellulitis	0.1	+++	++++	++++	−	−	−
D_3	Dermatitis	0.1	+++	++++	++++	−	−	−
E_1	Empyema	0.1	+++	+++	+++	−	−	−
M_2	Mastoiditis	0.1	+++	+++	++++	−	−	−
N_1	Sinusitis	0.1	++	+++	+++	−	−	−
N_{11}	Sinusitis	0.1	0	0	0	0	+	+++
N_{17}	Sinusitis	0.1	0	0	0	0	+	++++
P_1	Peritonitis	0.1	+++	+++	++++	−	−	−
SF_{32}	Scarlet fever	0.1	++	++	+++	−	−	−
SF_{58}	Scarlet fever	0.1	++	++	+++	−	−	−
T_{33}	Tonsillitis	0.1	++	+++	+++	−	−	−

0 indicates complete protection; ++++ signifies cutaneous lesion measuring 4 cm. in diameter or over, +++, 3 cm., ++ and +, 2 cm. and 1 cm., respectively; ± indicates doubtful reaction and − that no test was made.

emulsion, typical erysipelatous lesions developed at the site of injection, similar in nature to the lesions produced by the streptococci alone. No protection was offered by the normal rabbit serum or the heated immune serum against the pathogenic activity of the erysipelatous hemolytic streptococci. Large lesions developed in every inoculated area (Figs. 4 to 6).

tococci. The precision with which the degree of skin-reactions corresponded with variable mixtures of immune serum and streptococci seemed almost mathematical in nature when monovalent serum and its homologous culture were employed. Deviation from this precision was immediately apparent when heterologous strains of the same biological type of hemolytic

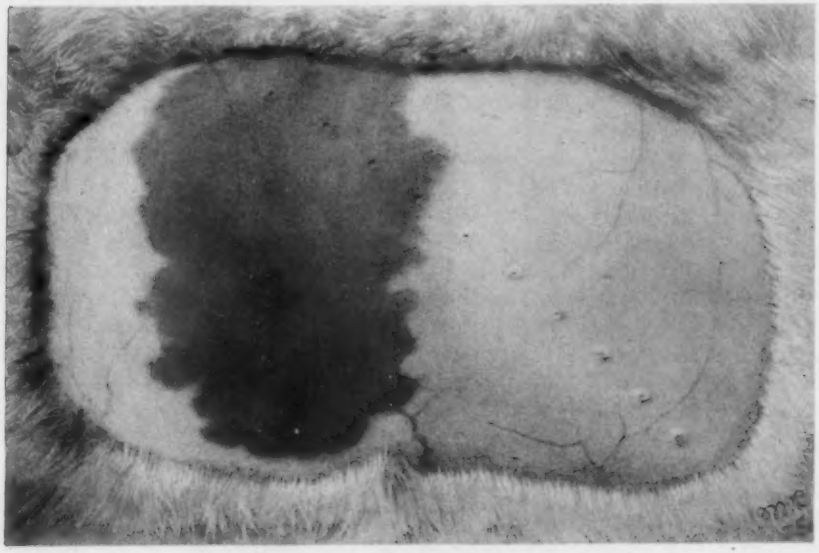

FIG. 10. REFRACTORY ZONE

Intradermal inoculations of 0.2 cc. emulsion of *Streptococcus erysipelatis* in 4 places (vertical line) and intradermal infiltrations of 0.1 cc. anti-erysipelas serum in 10 places (oblique line). Drawing made 12 hours later.

That the protection of the immune erysipelatous serum against the injurious action of the homologous culture which produced the serum is a quantitative phenomenon was clearly demonstrated by keeping the dilution of the immune serum constant and by increasing the dose of hemolytic streptococcus were made use of in order to demonstrate specific protection (Table II).

In a series of 78 protection experiments with immune erysipelas serum against its homologous or heterologous cultures, the smallest amount of immune serum which adequately pro-

tected against the injurious action of 0.1 cc. of streptococcic emulsion was found to be 0.005 cc. The average amount of immune serum which constantly protected 0.1 cc. of bacterial suspension was found to be 0.05 cc. Of practical significance in the serological differentiation of groups of hemolytic streptococci was the observation that immune erysipelas sera offered no protection against the injurious action intradermally of hemolytic streptococci isolated from sources other than erysipelas, such as cellulitis, dermatitis, empyema, peritonitis, tonsillitis or scarlet fever.

That the skin possesses a special biological function not shared by other tissues in the body has been suggested by the studies on the phenomenon of local passive immunity by Besredka (6), Gay (4), Mironesco (10) and many other investigators. Particularly important are the studies of Gay on local streptococcic immunity, which promise to become of practical significance in the preventive treatment of local infections. In our experiments it was observed that rabbits in which local passive immunity was conferred against the injurious action of erysipelatous streptococci, no specific agglutinins were found in the circulating blood-stream for the homologous or heterologous cultures which had produced the local passive "tissue resistance." It was likewise found that local passive immunity did not protect the animal against a lethal dose of the homologous culture when this was administered intra-peritoneally, intra-pleurally, or intravenously. These experiments will be discussed later in this report.

PASSIVE GENERAL IMMUNITY AGAINST THE ACTION OF ERYSIPELATOUS STRAINS OF HEMOLYTIC STREPTOCOCCI AFTER INTRAVENOUS ADMINISTRATION OF IMMUNE ERYSIPELAS SERUM

A series of 64 experiments were performed on normal rabbits to determine whether intravenous administration of immune erysipelas serum can protect the animal against the lethal dose of the homologous or heterologous culture of hemolytic streptococci. In the following experiments the immune erysipelas serum "B_3" was employed because of its high agglutinin titer. Since it was found in our earlier experiments (8) that 23 per cent of the average stock rabbits possessed natural agglutinins for the cultures of erysipelatous hemolytic streptococci, the serum of each animal was first tested against strains of of streptococci employed in these experiments. Any rabbit found to possess natural agglutinins was consequently discarded.

A series of 20 rabbits (Table III) were passively immunized with 5 cc. of the immune erysipelas serum "B_3", administered intravenously. Twenty-four hours after the injection of the immune serum these rabbits were inoculated intravenously with virulent erysipelatous hemolytic streptococci. The animals received a total dose of 2, 3, 4, or 5 cc. of an 18-hour broth culture, 2 cc. of which had already been established as a lethal dose per kilogram of body-weight. For control purpose, another series of normal rabbits were employed which had not received immune serum previous to

the intravenous inoculation of similar doses of virulent erysipelatous hemolytic streptococci as in the first series. Animals that survived these inoculations four days later were considered to be adequately protected by the immune serum.

protection against super-lethal doses of the homologous as well as of the heterologous cultures of erysipelatous streptococci when these were injected intravenously. Blood-cultures were made every 15 minutes after the intravenous inoculation of the streptococci

TABLE III

General protective power from intravenous administration of immune erysipelas serum "B_3" against strains of the homologous and heterologous erysipelatous streptococci

STRAINS	TYPE OF STRAINS	TYPE OF IMMUNE SERUM, INTRAVENOUS, 5 cc.	DOSE OF STREPTOCOCCUS (INTRAVENOUS)			
			2.0 cc.	3.0 cc.	4.0 cc.	5.0 cc.
B_3	Erysipelas	B_3	S.	S.	S.	S.
		No serum	D. 76 hours	D. 32 hours	D. 24 hours	D. 9 hours
C_1	Erysipelas	B_3	S.	S.	S.	S.
		No serum	S.	D. 37 hours	D. 21 hours	D. 11 hours
C_4	Erysipelas	B_3	S.	S.	S.	S.
		No serum	D. 16 hours	D. 21 hours	D. 14 hours	D. 8 hours
C_7	Erysipelas	B_3	S.	S.	S.	S.
		No serum	S.	D. 16 hours	D. 12 hours	D. 12 hours
C_{10}	Erysipelas	B_3	S.	S.	S.	S.
		No serum	D. 48 hours	D. 32 hours	D. 12 hours	D. 8 hours
N_2	Sinusitis. Recur. erys.	B_3	S.	S.	S.	S.
		No serum	S.	S.	D. 18 hours	D. 12 hours
D_1	Cellulitis	B_3	S.	D. 36 hours	D. 24 hours	D. 8 hours
		No serum	S.	D. 48 hours	D. 24 hours	D. 12 hours
SF_1	Scarlatina	S.F. "A_7"	S.	S.	S.	S.
	Scarlatina	B_3	S.	D. 24 hours	D. 12 hours	
		No serum	S.	D. 24 hours	D. 10 hours	

S. indicates that animal survived, D. that animal died, S.F. "A_7", Dochez' anti-scarlatinal serum. Recur. erys., signifies that patient presented a history of recurrent erysipelas. The dose of 5 cc. of immune serum was in each case administered intravenously 24 hours before the intravenous inoculation of virulent hemolytic streptococci. The bacterial emulsion was from an 18-hour broth culture.

The results of these experiments are shown in Table III. It was observed that the intravenous administration of immune erysipelas serum 24 hours before the inoculation with the virulent streptococci afforded complete

into animals previously immunized. It was found that the cultures became sterile from 45 minutes until an hour and a half after the bacterial inoculation of as high as 5 cc. of an 18-hour broth culture. None of the control

animals survived a dose of 3 cc. of the same streptococcic inoculum administered to the passively immunized rabbits. Blood-cultures made of the control animals yielded live streptococci from 2 until 46 hours after the injection of from 3 to 5 cc. of an 18-hour broth culture. This strongly suggested that the immune erysipelatous serum not only neutralized the toxic products of streptococcic secretion, but also played the rôle of a bactericidal agent.

When the streptococci were injected intramuscularly or intracutaneously 24 hours after the intravenous administration of the immune erysipelas serum it was likewise observed that adequate protection was obtained against the harmful effects of super-lethal doses of virulent hemolytic streptococci of erysipelatous origin. No protection resulted when the immune erysipelas serum was injected intravenously 24 hours before the intravenous, intramuscular or intracutaneous inoculation with non-erysipelatous hemolytic streptococci isolated from cases with cellulitis, dermatitis, empyema, peritonitis, sinusitis, tonsillitis or scarlet fever.

It was found that when a protective dose of 5 cc. of immune erysipelatous serum was injected intramuscularly on one side of the body, preferably into the thigh, and simultaneously a lethal dose of 5 cc. of erysipelatous hemolytic streptococci was injected intramuscularly on the other side of the body, the animal displayed severe toxic symptoms as early as eight hours after the inoculation, but recovered rapidly during the following twelve hours. On the other hand, when a protective dose of 5 cc. of immune serum was mixed with the lethal dose of 5 cc. of streptococci and immediately injected intramuscularly, no toxic symptoms developed. It was apparent from these studies that a general dissemination of antibodies was best and most rapidly accomplished through the intravenous route, or by injecting the immune serum directly into the area infected with the streptococcic inoculum. Results of experiments of this nature prove that the anti-erysipelas serum is bactericidal as well as protective in behavior, since the injected bacteria ceased to be pathogenic shortly after the union was established between the antigen and its antibody, to the extent that no toxic symptoms developed (Fig. 11).

CLINICAL APPLICATIONS

It has already been demonstrated that no antigenic relationship existed between strains of hemolytic streptococci associated with scarlet fever and erysipelas. Immune erysipelas serum has been found to offer no protection against strains of scarlatinal streptococci and vice versa. In previous studies concerning the rash extinction phenomenon in scarlet fever (15), it was pointed out that whereas Dochez' anti-scarlatinal serum produced the Schultz-Charlton reaction in 100 per cent of early scarlet fever rash, Dochez' serum failed to produce the blanching phenomenon in seven cases of erysipelas. To this series have since been added 12 cases of erysipelas, in which further intradermal injections of Dochez' anti-scarlatinal serum failed to produce any perceptible change in the erysipelatous lesion. It seemed desirable to examine the effect of the immune rabbit erysipelas serum when

it was injected intradermally in the rash of scarlet fever. A dose of 0.1 cc. of immune erysipelas serum was injected intradermally in 17 cases of scarlet-fever rash. In close proximity to the area infiltrated with anti-erysipelas serum, a similar dose of Dochez' serum was injected intradermally. In no instance was the blanching phenomenon observed in the areas infiltrated with the anti-erysipelas serum, whereas Dochez' serum produced the rash extinction reaction in 94 per cent of the cases tested (Fig. 12).

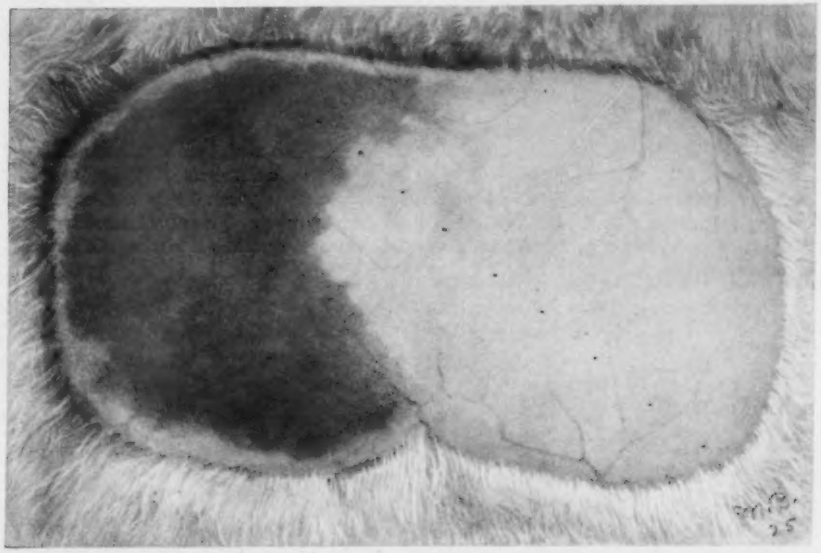

FIG. 11. SAME AS FIG. 10, AS SEEN 36 HOURS AFTER INJECTION OF STREPTOCOCCI AND ANTI-ERYSIPELAS SERUM

Note extension of erysipelatous lesion to the left and the refractory zone produced along the passively immunized oblique line.

Intradermal, intravenous and intramuscular injections of large therapeutic doses of immune rabbit serum have been resorted to in several cases of severe erysipelas. The therapeutic results obtained both locally and generally with the anti-erysipelas serum are promising. With the production of immune erysipelas serum in horses, these studies will be continued with higher concentration and larger quantities of serum.

DISCUSSION

In these studies no effort has been made to render a complete biological classification of the Streptococcus erysipelatis. Available methods by which to determine antigenic differences between groups of hemolytic streptococci prohibit at once such a complex task. An attempt has been made in this report to differentiate antigenically between strains of hemolytic streptococci isolated from a great variety of streptococcic infections,

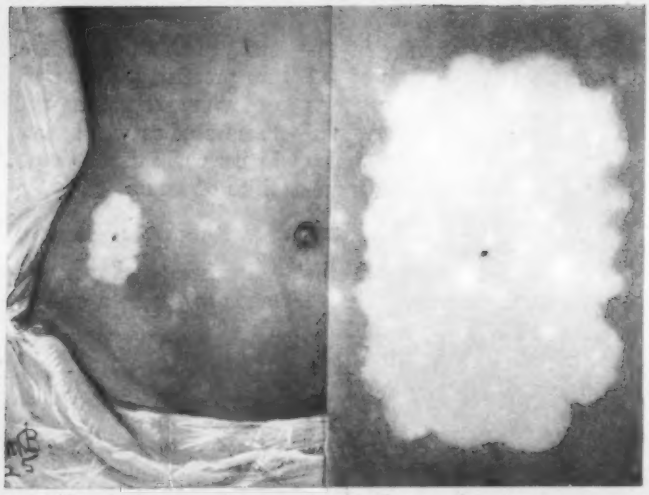

FIG. 12. SCARLET FEVER, SECOND DAY OF DISEASE

Intradermal infiltration of 0.1 cc. pneumococcus serum (upper), 0.1 cc. anti-erysipelas serum (middle) and 0.1 cc. Dochez' anti-scarlatinal serum (lower). Blanching phenomenon observed 9 hours after infiltration of Dochez' anti-scarlatinal serum. Other areas negative.

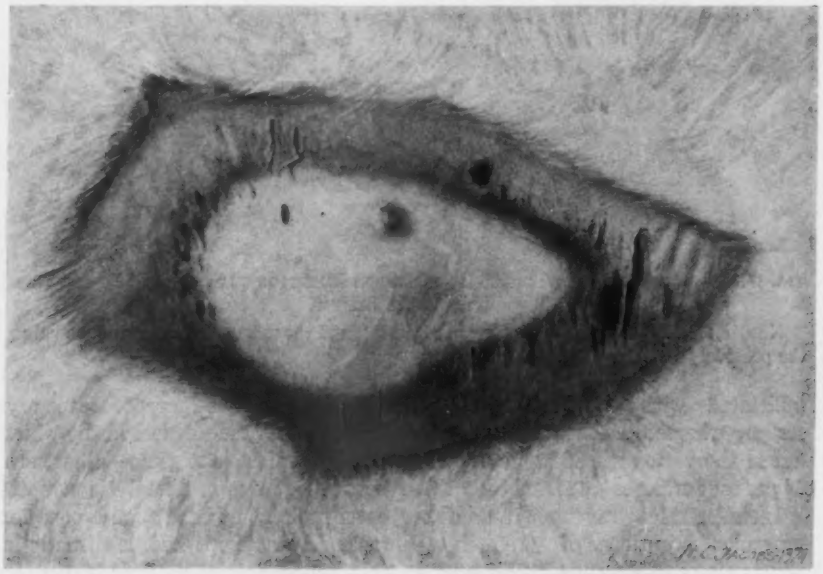

FIG. 13. ERYSIPELATOUS LESION PRODUCED IN SKIN OF RABBIT AFTER INTRADERMAL INOCULATION OF 0.5 CC. EMULSION OF STREPTOCOCCUS ERYSIPELATIS

Twenty-four hours later injected intradermally 1.0 cc. of anti-erysipelas serum in the center of the lesion. Blanching phenomenon observed 24 hours after serum infiltration. Small abscess produced within the blanched area by subsequent intradermal inoculation of 0.2 cc. emulsion of *Streptococcus erysipelatis*. No erysipelatous lesion developed.

such as cellulitis, dermatitis, empyema, peritonitis, sinusitis, scarlet fever and erysipelas. The main concern has been an intensive study of streptococci associated with erysipelas and scarlet fever.

If the original conclusions advanced by Castellani in 1902 (16) concerning agglutination and agglutinin absorption form a correct basis for bacterial identification, then we were able to demonstrate that 91.2 per cent of erysipelas strains of hemolytic streptococci fall antigenically into one group and that this group of streptococci can be readily differentiated by the same methods from strains of hemolytic streptococci isolated from scarlet fever, cellulitis, empyema, peritonitis, sinusitis, puerperal sepsis, tonsillitis, and a number of other streptococcic infections. The work on opsonins by Ruediger (17), Schorer (18), Tunnicliffe (19) and Boughton (20), and likewise the study of agglutination by Tunnicliffe (19) suggested that such a group of hemolytic streptococcus existed. The comprehensive investigations of Dochez, Avery and Lancefield (21) on the biology of Streptococcus hemolyticus, with particular reference to agglutination and protection, strongly suggested that cultures of streptococci isolated from cellulitis, erysipelas and septicemia differed among themselves antigenically and possibly fell into individual groups, although no definite conclusions were advanced concerning type specificity of these strains of streptococci. But further work seemed imperative before the classification of Streptococcus erysipelatis by *in vitro* methods could be substantiated.

Recent criticism of *in vitro* methods as criteria for bacterial identification has mainly been directed against the "two-phased phenomenon" of combination of agglutinin and bacterium, and spontaneous flocculation through physical action. Krumwiede, Copper and Provost (11) in their comprehensive review of the subject of agglutinin absorption, have adequately focussed attention on the doubtful value of *in vitro* methods. To overcome this adverse criticism, the author resorted to demonstration *in vivo* of local and general protection by immune sera in order to determine specificity of strains of hemolytic streptococci. It was readily seen at the very beginning of the studies on active immunity, and later by the *in vivo* protection tests, that these methods not only served the purpose of demonstrating antigenic differences between groups of hemolytic streptococci, but also suggested the therapeutic advantages for warding off the injurious action of virulent streptococci either by local infiltration of the healthy skin with immune serum or by intravenous or intramuscular administration of larger doses of immune serum for the neutralization of the general toxic symptoms.

SUMMARY

1. Intracutaneous inoculation of hemolytic streptococci isolated from human cases of erysipelas produced typical erysipelas-like lesions in the skin of normal and susceptible rabbits. Three types of lesions were observed—erythematous, diffuse and phlegmonous. The pathological picture of the erythematous and diffuse lesions was similar in nature to that seen in human cases of erysipelas.

2. Intracutaneous infiltration of

mixtures of immune erysipelas serum and hemolytic streptococci of erysipelas origin afforded local protection against the injurious action of the streptococci. Normal rabbit serum or immune erysipelas serum heated at 60° C. for 30 minutes failed to protect the skin against the harmful effects of the inoculated erysipelatous streptococci.

3. Intravenous or subcutaneous administration of large doses of immune erysipelas serum protected the animal against lethal doses of hemolytic streptococci isolated from erysipelas, when the serum was injected 24 hours before the bacterial inoculation. Normal rabbit serum or immune erysipelas serum heated at 60° C. for 30 minutes offered no protection against the lethal dose of erysipelatous streptococci.

4. Immune erysipelas serum afforded no local or general protection against the harmful action of hemolytic streptococci isolated from non-erysipelas sources.

5. Intradermal infiltration of Dochez' anti-scarlatinal serum produced the blanching phenomenon in the rash of 94 per cent of scarlet fever patients, whereas similar infiltration of anti-erysipelas serum failed to produce the blanching phenomenon in the rash of scarlet fever.

6. Intradermal, intravenous and intramuscular injections of large doses of immune erysipelas serum in cases of erysipelas seem to offer promise for the specific treatment of the disease.

I take pleasure in expressing my gratitude to Mr. Max Broedel for the illustrations, which in part were drawn from the author's protocol-sketches. I am also deeply indebted to Dr. Edward McP. Armstrong, whose generous gift rendered possible the publication of the illustrations.

REFERENCES

(1) Fehleisen: Die Aetiologie des Erysipels, Berlin, 1883.

(2) Roger, G. H.: *Compt. rend. Soc. de biol.*, 1890, xlii, 573.

(3) Grammakowsky, D.: *Ann. de l'Inst. Pasteur*, 1895, ix, 620.

(4) Gay, F. P.: *Jour. Lab. and Clin. Med.*, 1918, iii, 721.
Gay, F. P., and Rhodes, B.: *Jour. Infect. Dis.*, 1922, xxxi, 101.
Gay, F. P., and Morrison, L. F.: *Jour. Infect. Dis.*, 1923, xxxiii, 338.
Gay, F. P.: *Jour. Immunol.*, 1923, viii, 1; *Physiol. Rev.*, 1924, iv, 191.

(5) Denys, J., and Leclef, J.: *La Cellule*, 1895, xi, 177.

(6) Besredka, A.: *Tr. Roy. Soc. Trop. Med. and Hyg.*, 1923–24, xvii, 346; *Presse méd.*, 1924, xxxii, 585.

(7) Rivers, T. M.: *Jour. Exper. Med.*, 1925, xli, 179.
Rivers, T. M., and Tillett, W. S.: *Jour. Exper. Med.*, 1925, xli, 185.

(8) Birkhaug, K. E.: *Proc. Soc. f. Exper. Biol. & Med.*, 1925, xxii, 292; *Bull. Johns Hopkins Hosp.*, 1925, xxxvi, 248.

(9) Neisser, M., and Lubowski, R.: *Cntrlbl. f. Bakt.*, Orig., 1901, xxx, 483.

(10) Mironesco, T.: *Compt. rend. Soc. de biol.*, 1925, xcii, 293.

(11) Krumwiede, C., Cooper, G., and Provost, D. J.: *Jour. Immunol.*, 1925, x, 55.

(12) Taylor, F. E.: *Jour. Hyg.*, 1918, xvii, 415.

(13) Breinl, F., and Fischer, M.: *Ztschr. f. Immunforsch.*, 1922, xxxv, 205.

(14) Turro, R., and Domingo, P.: *Compt. rend. Soc. de biol.*, 1923, lxxxviii, 410.

(15) Birkhaug, K. E.: *Jour. Clin. Invest.*, 1925, i, 273; *Bull. Johns Hopkins Hosp.*, 1925, xxxvi, 134.

(16) Castellani, A.: *Ztschr. f. Hyg.*, 1902, xl, 1.

(17) Ruediger, G. F.: *Jour. Am. Med. Assn.*, 1906, **46**: 108.

FIG. 11. ERYSIPELAS, THIRD DAY OF DISEASE.

Infiltration of 1 cc. anti-erysipelas serum subcutaneously and 0.5 cc. intradermally on the left side of forehead and similar injections of Dochez' anti-scarlatinal serum on the right side of forehead. Fading of erysipelas lesion, with disappearance of edema and tenderness in the area infiltrated with anti-erysipelas serum when observed 11 hours after serum infiltration. Area infiltrated with Dochez' anti-scarlatinal serum remained negative.

(18) Schorer, E.: *Am. Jour. Med. Sc.*, 1907, cxxxiv, 728.

(19) Tunnicliffe, R.: *Jour. Infect. Dis.*, 1907, iv, 304; *ibid.*, 1908, v, 268; *Jour. Am. Med. Assn.*, 1920, 75: 1339.

(20) Boughton, T.: *Tr. Chicago Path. Soc.*, 1909, viii, 24; *Jour. Infect. Dis.*, 1910, vii, 110.

(21) Dochez, A. R., Avery, O. T., and Lancefield, R. C.: *Jour. Exper. Med.*, 1919, xxx, 179.

Congenital Duodenal Septum with Obstruction

By S. M. Seidlin

From the Department of Pathology, The Johns Hopkins University, Baltimore

INTRODUCTION

CONGENITAL occlusions of the small intestines are to be grouped with the rarer forms of congenital malformations. Emil Theremin (1), for instance, in 1877, found only two cases of such malformations on record among 111,451 children admitted to the Vienna Foundling Hospital during a period of 11 years, and 9 cases among 150,000 admitted to the St. Petersburg Foundling Hospital for a period of 20 years.[1] He failed to find any such cases in the records of the foundling hospitals of Moscow and Prague. In 1900, J. Tandler could collect from the literature only 94 cases of intestinal occlusion, exclusive of anal atresias. Out of these, 33 occurred in the duodenum, 55 in the jejunum and ileum, and 6 in the colon. Disregarding the 6 cases in the large intestine, the following proportions present themselves for the atresias in the small intestine: 37.5 per cent of these were in the duodenum, and 62.5 per cent in the jejunum or ileum. According to this, the probability that an atresia occurring in the small intestine will be located in the duodenum would be slightly more than 1:2. When one considers that the length of the small intestine of the newborn is 5.3 m. (Vierordt), while that of the duodenum is only about 15 cm. (Tandler), it is quite apparent that the duodenum has a peculiar predisposition for congenital atresias. Karpa (2), in 1906, collected 49 cases of duodenal stenoses and atresias. Out of 39 cases in which the exact location of the occlusion was indicated, there were 29 (74 per cent) with the malformation either at the site of opening of the ductus choledochus or in its immediate vicinity.

The occlusions are usually single, but occasionally in the jejunum and ileum they are multiple. They vary greatly in degree, from slight strictures to complete obliterations of the intestinal lumen. Occlusions by perforate iris-like septa stretched across the lumen of the duodenum at the site of the ampulla of Vater are by far the rarest but more interesting variety. The case here reported is an example of this type of duodenal occlusion. It appears that in the present case also the child was older than any other in the several similar cases on record where the malformation was definitely shown to have been the cause of death.

[1] All the children who had died in the latter institution were subjected to post-mortem examination.

Clinical history. (By courtesy of Dr. J. Howland.) M. S. (H.L.H. No. 39063), a colored girl, 2½ years of age, was admitted to the Harriet Lane Home on January 26, 1924. The chief complaint was vomiting and constipation.

Past history. Full-term baby. Normal delivery. She was breast fed until 14 months of age. From 14 to 18 months the child continued nursing, with the addition of whole cow's milk, cereals, and orange juice. After 18 months the diet consisted of milk, cereals, vegetables, fruits, and meats. She seemed to develop normally. She had had varicella at 2 years of age andhad always been subject to constipation.

Present illness. She had been perfectly well until three days before admission. The only unusual item in her diet had been some canned corn, which she had eaten about two weeks before. She appeared to be well and played as usual until three days prior to admission, when the mother noted that the abdomen had increased in size, and seemed "knotted up." The following day she vomited several times some brownish material and food. She continued to vomit everything that was given to her, complained of abdominal pain, and for three days retained no food. A physician discovered some small kernels of corn in the vomitus, a sample of which was brought to the hospital with the child. On rigid questioning it was learned that the child had been given corn in her diet only once—two weeks prior to admission—and ten days before the onset of symptoms.

Physical examination on admission. A fairly well developed colored child, 2½ years of age, seemed bright, noticed objects and people. The skin was loose, showing recent loss of weight. The abdomen was full, but no rigidity or resistance could be detected. The liver edge was felt one finger's breadth below the costal margin. The spleen was not palpable. On deep palpation a distinct mass, somewhat smaller than a hen's egg, could be felt on each side of the midline, below the level of the umbilicus. The mass on the right was larger and more definite than on the left, and both were slightly nodular in outline. The physical examination was otherwise negative. Temperature, 99°. Urine, negative. Leucocytes, 19,600.

Course in the hospital. On the day of admission, an enema was given. This returned clear, except for a slight brownish coloring. She took three ounces of milk well, and did not vomit. The day after admission a high colonic irrigation with 1500 cc. of warm water returned only slightly colored. She took 6 ounces of whole milk fairly well. There was no vomiting. A soap-suds enema that evening was effectual.

She continued to take her milk well, was given a soft diet, and three days after admission was seen in consultation by the surgical staff, who concluded that there was no intestinal obstruction. An enema at this time yielded a large amount of fecal material, and she was given white oil. Five days after admission, she had gained weight, stood up in bed, and seemed in no discomfort. She was then given a regular diet. That evening she was quite distended, and large peristaltic waves were noted. An enema yielded a large amount of fecal material.

On the sixth day she was still distended and large peristaltic waves in the upper abdomen were noted. She was put on a soft diet. On the seventh day after admission her appetite was poor and she vomited once. Instead of the soft diet she was given 5 ounces of whole milk. Her condition was otherwise the same.

On the morning of the eighth day after admission, her temperature was 95.6°. She had lost two pounds in 24 hours, was weak and listless, with eyes sunken and abdomen scaphoid. She was given an enema which was effectual. One hour later she seemed somewhat weaker, and her pulse was hardly palpable. She made no response to external surroundings. Intravenous therapy was attempted but the veins were collapsed, and her arteries could not be palpated, even after successive doses of adrenaline. She was given a mixture of 200 cc. of normal saline and 200 cc. of 5 per cent glucose intraperitoneally, but twenty minutes later she was in complete collapse, and soon died.

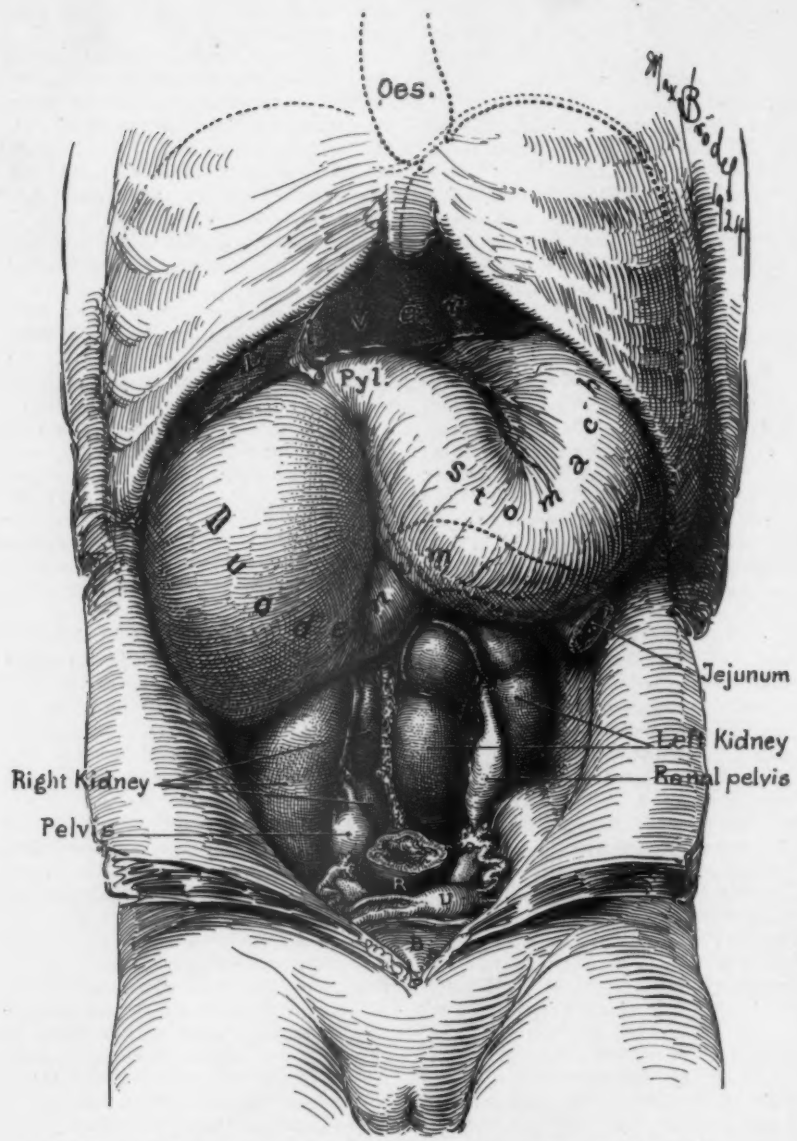

FIG. 1. APPEARANCE OF THE ABDOMINAL CAVITY DURING AUTOPSY

AUTOPSY FINDINGS

The *autopsy* (No. 7886) was performed 3½ hours after death. The body was that of a young, well nourished, colored girl, measuring 98 cm. in length and weighing 13.5 kilograms. Rigor mortis was well developed.

The abdomen was markedly distended and soft on palpation. When opened, the cavity was found to contain about 500 cc. of clear, colorless fluid (intraperitoneal injection). The peritoneal surfaces were smooth and glistening, and nowhere thickened. There were no adhesions. The greater omentum and mesentery were normal. The stomach and the duodenum, especially the latter, were extraordinarily distended, and presented a very striking picture (Fig. 1). The small intestines were of a pale pink color and showed several intussusceptions, which, because of lack of any pathological changes in the intestinal wall involved, were unquestionably postmortem in origin. The lower half of the small intestines seemed to be of very small diameter in comparison with that of the first half. The colon was normal. The liver extended about 2 cm. below the costal margin and appeared to be normal. The spleen was high under the diaphragm but showed no abnormalities. The pancreas, except for the pancreatic duct described below, was normal. Both kidneys were extremely malformed. They appeared as irregular masses of tissue lying on the pelvic brim near the bifurcation of the aorta (Fig. 1).

The pleural cavities contained no fluid. The pleural surfaces were smooth and glistening. There were no adhesions. The lungs were normal in every respect. The pericardial cavity contained a little fluid. The surfaces were smooth and there were no adhesions. The heart and aorta were normal. One of the coronaries, however, took origin 0.5 cm. above the upper level of the aortic valves. The mediastinal lymph nodes were not enlarged. The thymus was of about normal size for a child of 2½ years.

Since the alimentary tract and the kidneys were the only organs that presented unusual features, we shall confine ourselves to a description of these in detail. Permission for the examination of the brain was not obtained.

Gastro-intestinal tract. The jejunum was tied near the beginning of its course and cut through caudad to the ligature. The oesophagus, stomach, duodenum and a small portion of the jejunum were removed intact together with the liver and the pancreas. The gastric and duodenal contents, which consisted of a watery white suspension, were allowed to run out through the oesophagus. Formaldehyde solution was then injected through the same oesophageal opening until the stomach and duodenum had reached their original size, after which the oesophagus was tied with a string, and the whole specimen immersed in formalin. After this procedure it was noticed that the small portion of the jejunum which was still attached to the duodenum and of a normal diameter before the injection of formalin, was now moderately but distinctly distended. A week later the oesophagus, stomach, duodenum, and the attached portion of the jejunum were opened.

The *oesophagus* was distended in the lower two-thirds of its length to a diameter of about 5 cm. The oesophageal wall was normal. The cardiac opening of the stomach measured about 1 cm. in diameter.

The *stomach* was extremely distended; the greatest diameter being 7.5 cm. The lesser curvature measured 13.5 cm. in length, the greater curvature 39 cm. The gastric wall was very much thickened, but no other change was found on gross inspection. The pylorus was wider than normal, about 1.8 cm. in diameter. There was a fold of mucosa just above the pylorus which encroached somewhat upon its lumen.

Duodenum. The so-called first or superior portion was not present as a distinct hepatic angle of the duodenum. It had apparently become incorporated in the second or descending portion, and we shall, therefore, describe them together as the descending portion of the duodenum. The duodenum, which at autopsy was even larger than the stomach, was most distended in its descending portion, reaching a diameter of 8 cm. The distended part was bent on itself and gradually narrowed

FIG. 2

Upper sketch: Oesophagus, stomach and duodenum opened after fixation in formalin.
Lower sketch: Duodenal lumen with septum shown from the jejunal side.
Drawing in upper left corner: Diagrammatic representation of the course of the biliary and pancreatic ducts in relation to the duodenal septum, its surfaces and orifice.

down as it approached the duodeno-jejunal angle, at which point the diameter rather abruptly approached that of the normal jejunum. The duodenum was almost completely surrounded by peritoneum, except for the part adherent to the pancreas and a small area on the posterior surface. When opened, the duodenum was found to be divided into two parts by a septum stretched across the lumen, about 10 cm. above the jejunal flexure and 10.5 cm. from the pylorus along the "lesser curvature" of the duodenum. At this point it was about 5 cm. in diameter. The proximal portion (the part of the duodenum above the septum) was larger than the distal portion, its wall considerably thickened, and lined with pale, normal-appearing mucosa. The wall of the distal portion of the duodenum was not thickened. Its mucosa was green in color, unquestionably bile-stained.

The outer surface of the duodenum at the site corresponding to the septum showed no constriction except for a slight short groove on the anterior outer surface.

The septum itself was dome-shaped, with the convexity directed toward the jejunum (Fig. 2). In its most convex portion there was an eccentrically placed opening, about 7 mm. in diameter, situated somewhat posteriorly and cephalad to the center of the septum. At and around the opening the septum was thickened and of a denser consistence. The lumen of the opening was completely plugged with semi-solid, stringy food material which projected on both sides of it. On the gastric side of this plug there were several kernels of corn and one bean.

The common bile-duct (Figs. 2, 3, 4) was about 5 mm. in diameter. The distal part was narrower. It could be followed for some distance between the head of the pancreas and wall of the duodenum, and

FIG. 3. STOMACH AND DUODENUM SHOWN WITH THE LIVER RETRACTED UPWARD SO AS TO EXPOSE THE COURSE OF THE COMMON BILE-DUCT BEFORE IT ENTERS THE DUODENUM

FIG. 4. SECTION THROUGH THE DUODENUM (D-1, D-2) AND POSTERIOR PART OF THE SEPTUM (S) NEAR ITS ORIFICE, ACROSS THE COMMON BILE-DUCT (C.B.D.) AND PANCREATIC DUCT (P.D.)

D-1, duodenal wall on the proximal side of the septum. D-2, duodenal wall on the distal side of the septum. A small piece of pancreatic tissue (P) is attached to the duodenum. (Hematoxylin and eosin, × 2.)

then, entering the wall of the duodenum itself, it finally came to lie between the two surfaces of the septum. It opened into the lumen of the duodenum on the distal or jejunal surface of the septum, very close to the margin of the septal opening, in a groove formed by folds of mucosa. These folds of mucosa extended from the duodenal wall to the septal opening, and having reached the latter, diverged to surround it. There were no such folds on the gastric surface of the septum.

The pancreatic duct (see Figs. 2, 4) also passed into the duodenal septum between its two layers of mucosa for a distance of several millimeters and then opened into the lumen of the duodenum on the gastric surface of the septum at a point midway between the posterior margin of the septum and its central orifice. Since this single pancreatic duct had no communication with the biliary duct, and since it was situated cephalad to the latter, we may presume that it was the duct of Santorini.

The jejunum, ileum, appendix, colon and rectum were normal. The Peyer's patches were enlarged and injected. The mesentery showed no abnormalities, except for markedly enlarged mesenteric lymph nodes.

Kidneys. The kidneys were extremely malformed (Fig. 1). The lower poles were on the same level below the brim of the pelvis. The upper pole of the left kidney was about 1.5 cm. higher than that of the right. The distance between the lower poles of the kidneys and the bladder was about 7 cm.

The left kidney weighed about 40 grams and measured 7 × 4.5 × 2.5 cm. It was larger than the right, which weighed about 30 grams and measured 5.5 × 4.5 × 3 cm. They were somewhat flattened out in the antero-posterior diameter and both showed marked lobulation. The kidneys had apparently failed to ascend and to rotate inwardly. The pelves were extrarenal and situated on the anterior surface of the kidneys. Each pelvis appeared as a pear-shaped dilatation of the upper end of the ureter. The left pelvis was connected with its kidney by three narrow tubes, the right pelvis by two. The kidneys were supplied by three pairs of arteries coming off the abdominal aorta and the iliac arteries, and drained by several veins into the inferior vena cava. The capsule of each kidney stripped off easily, leaving a smooth, pale pink surface. On section the cortex was normal with rather prominent bright red glomeruli. The pyramids were normal. The calyces converged to the tubes which connected the kidneys with their respective pelves. One of the calyces

in the right kidney contained a renal calculus measuring 5 × 3 × 2 mm. Both ureters were short and patent. Their mucosa, as well as that of the pelves, was normal. The urinary bladder was normal except for some small haemorrhages in the mucosa.

Microscopical notes. Section through the pylorus including the stomach wall and the duodenum: Except for considerable thickening of the mucosa and of the circular muscle layer, the gastric wall is normal. There is also thickening of the mucosa and of the longitudinal muscle layer of the duodenum.

Section through the posterior part of the septum near its orifice, across the common bile-duct and the pancreatic duct (see Fig. 4): This section shows a segment of the duodenum (D-1, D-2) with the septum (S) stretched across. A small piece of pancreatic tissue (P) is seen attached to the wall of the descending portion of the duodenum. The circular layer of muscle in the duodenum on the gastric side of the septum and at the septal margin shows marked hypertrophy. A considerable number of Brünner's glands are seen throughout the duodenal mucosa. The septum at the level of the section is 3.5 cm. in diameter. It consists of two layers of typical duodenal mucosa with one of loose areolar submucous tissue in between. Brünner's glands are also present on both sides of the septum. In its upper portion the circular muscle layer extends down into the septum for a distance of about 7 mm. Between these muscle fibres and the duodenal mucosa of the gastric side of the septum the pancreatic duct (P.D.) is seen. The mucosa on the jejunal side of the septum, when reaching about the middle of the latter, is thrown up into numerous folds which surround the opening of the common bile-duct (C.B.D.).

Section through the anterior part of the septum: A T-shaped section was made through this part of the septum including the duodenal wall on each side. The septum consists of two layers of apparently normal mucosa, with Brünner's glands in both its layers, and a layer of loose areolar tissue between. The duodenal wall on the gastric side of the septum, and at the level of the latter, shows marked hypertrophy of the circular muscle layer. The duodenal wall on the jejunal side is of normal thickness.

Sections of both kidneys: Microscopical study of the renal tissue revealed no abnormality.

Section of bladder wall: The crests of some of the larger mucosal folds show small recent haemorrhages.

DISCUSSION

The post-mortem examination clearly demonstrated that the intestinal obstruction was responsible for the death. The child had lived an apparently normal life for two and a half years in spite of the duodenal septum. It is clear that while she was being breast fed and later maintained on a soft diet, the food passed easily through the small orifice in the septum. The ingestion of coarser food material had produced the acute obstruction at this orifice.

The most interesting question that comes up in connection with this case is that of the etiology of congenital intestinal occlusions, in general, and of the duodenal septum, in particular. Numerous hypotheses have been suggested. Some of them attribute atresias and stenoses to anomalies in development, others to pathological changes. Most of them, however, are calculated to help in the elucidation of only single cases, and do not serve to explain others. There are references, for instance, to tumor, enlarged liver, or swollen glands pressing upon the intestine, pressure by the mesocolon transversum, persistence of the omphalo-mesenteric duct, twisting of the umbilical cord, circumscribed inflammation or ulceration of the intestine, hypertrophy of mu-

cosal folds, circulatory anomalies, lack of biliary secretion, and even to psychic excitement of the mother. The more commonly stated hypotheses refer to occlusion of the superior mesenteric artery, twisting of the gut, chronic enteritis or peritonitis caused by syphilis or tuberculosis of the parents, or various infectious diseases of the fetus itself, and to intussusception.

In our case the mesenteric arteries were not occluded and, in general, thrombosis and embolism are practically unknown in fetal life. As to the twisting theory, although twisting might produce atresias in the jejunum and ileum, it is unlikely that the short mesentery of the duodenum, which is present during a part of fetal life, would permit twisting of this portion of the intestine. Although such twisting of the duodenum is conceivable, it certainly cannot account for the relatively frequent occurrence of duodenal occlusions. Besides, twisting is not likely to produce a septum of the kind described above. It is also unlikely that any inflammatory process is the etiological factor, for the duodenum in our case, as well as in those of others, does not show any signs of inflammatory reaction in any of its layers. Some authors maintain, however, that peritonitis can occur in the fetus without leaving the usual changes behind it.

As to intussusception as the possible cause of congenital intestinal occlusions, it was undoubtedly the actual cause of occlusion in a few reported cases in which remains of the necrotic invaginated portion of intestine could still be demonstrated. In our case, however, no trace could be found that would suggest an intussusception during fetal life. Of course, an early slight telescoping of the mucosa with a fixation of the surrounding tissues might indeed leave a septum without any evidence as to the mode of its formation.

J. Tandler (3) in his study, in 1900, on the early embryology of the human duodenum found that its lumen, in embryos between thirty to sixty days, is more or less completely closed by proliferating intestinal epithelium, but reopens later. In view of this, he interpreted the congenital atresias and stenoses as persistent embryonic structures. E. Krueter, in 1905 (5), and 1909 (6), and H. Forssner (4), in 1907, confirmed Tandler's observations not only for human embryos but also for those of other vertebrates. Kreuter expressed the generalisation that all congenital stenoses and atresias of the human digestive tract are to be traced back to embryonic occlusions, and should be regarded as physiologic and phylogenetic phenomena. On the other hand, H. Schridde (7), in 1909 examined 50 embryos of stages corresponding to those described by Tandler and Kreuter, but failed to find epithelial occlusions in any part of the intestinal tract.

The duodenum in general, and especially its portion at the level of the ampulla of Vater, shows a peculiar predisposition for congenital occlusions. This is not surprising when one considers that the second part of the duodenum presents during one period of embryonic life a relatively small area where numerous growth activities come into play. The pancreatic and liver *Anlagen* appear as diverticula of the enteric tube. The proximal

outgrowth of the hypoblast lining of the duodenum gives rise to a part of the pancreas with the duct of Santorini, and the distal outgrowth forms the primitive hepatic duct out of which develop the liver and the rest of the pancreas with the duct of Wirsung. A disturbance of the normal processes is more likely to occur here than, for instance, in such an area as the jejunum, where no such complexity in development exists. In this sense the duodenum is analogous to the cephalic end of the enteric canal where, too, the complexity of developmental factors is associated with the frequent occurrence of congenital malformations.

Although it seems probable that the same type of congenital intestinal occlusion can be brought about by varied causes, congenital intestinal occlusions in the region of the common bile and pancreatic ducts represent a distinctly characteristic group, in the formation of which similar factors are likely to be at work in every case. In particular reference to the perforate duodenal septum, there can hardly be any doubt of its being a true congenital malformation, in view of its peculiar make up, and its localization where other types of malformations occur. In the region of the second portion of the duodenum one not infrequently finds diverticula, for instance, anomalies in the bile and pancreatic ducts, accessory livers and accessory pancreas. Besides, duodenal septa are frequently associated with defects of other organs, defects that are distinctly developmental. In our case the duodenal septum is associated with congenitally malformed unascended kidneys. It is interesting in connection with the Tandler theory that both malformations hark back to the same stage of embryonic development; at the sixtieth day, when the duodenal lumen begins to be reestablished, the kidneys are still situated near the brim of the pelvis.

The literature contains several cases in which death could be ascribed directly to a congenital septum in the duodenum. The septum either had no opening at all, or only a very small one. The children died soon after birth. In the case recorded by Buchanan (8) the septum was situated just above the bile duct, it had a central aperture 2.5 mm. in diameter, and the child lived eighteen months. There had been no symptoms until three weeks before death, when attacks of vomiting had set in. The duodenal septum in our patient had a central orifice 7 mm. in diameter. The child lived two and a half years. She was free from symptoms until eleven days before death when vomiting and constipation began.

There is mention in the literature of eight cases of duodenal septa in adults (13) (14) (15) (16) (17) (18). Except for the most recent two cases, the description of them is rather meagre and incomplete. But as far as the evidence goes, in none of the cases was the diagnosis made during life. In practically every case, where a description was given, the portion of the duodenum above the septum, the pyloric ring, the stomach and the lower part of the oesophagus were found to be considerably dilated and and their walls thickened. In 4 out of the 8 cases it was indicated that the septum was located near the ampulla of Vater, in one case at the duodeno-

jejunal angle, and in three cases the exact location of the septum was not stated. The orifice of the septum in one case measured about 5 x 3 mm., in four cases it was larger than 7 mm. in diameter, and in three cases the size of the opening was not given. In some of these cases there were no gastro-intestinal symptoms at all; in others mild intermittent symptoms of high intestinal obstruction appeared in late childhood or adult life and gradually increased in severity and constancy. In none of them was the duodenal septum shown definitely to have been the immediate cause of death.

Cases of megaduodenum in adults have been reported by Ochsner (9), Finney (10), Bloodgood (11, 12), and others. Most of these cases were observed during operations, and those that came to autopsy showed no congenital membrane. The dilatation of the duodenum was explained in some as a result of compression by the root of the mesentery, by sphincters in the duodenum, by sharp kinks at the duodeno-jejunal angle, while in others no definite cause was demonstrable. But in view of the above eight recorded cases of duodenal septa in adults, it appears that the orifice in a congenital duodenal septum of the type described in the present case may be large enough to enable its possessor to live on to adult life and then be either suddenly or periodically occluded by food material, with the production of a megaduodenum. Such a membrane, if diagnosed *intra vitam*, might be amendable to surgical treatment.

I am greatly indebted to Mr. Max Brödel for the excellent drawings.

REFERENCES

(1) Theremin, Emil: Ueber congenitale Occlusionen des Dunndarms. *Deutsche Ztschr. f. Chirurgie*, 1877, vii, 33–71.

(1) Karpa, Paul: Zwei Fälle von Dünndarmatresie. *Virchow's Arch.*, 1906, clxxxv, 208–226.

(3) Tandler, Jul.: Über die Entwicklung des menschlichen Duodenums in frühen Embrionalstadien. *Morphol. Jahrbuch.*, 1900, xxix, 187–216.

(4) Forssner, Halmar: Die angeborenen Darm- und Oesophagusatresien. *Anatom. Hefte*, Nr. 102, 1907.

(5) Kreuter, Erwin: Die angeborenen Verschliessungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte. *Deutsche Ztschr. f. Chirurgie*, 1995, lxxix, 1–89.

(6) Kreuter, Erwin: Zur Aetiologie der congenitalen Atresien des Darms und Oesophagus. *Arch. f. klinische Chirurgie*, 1909, lxxxviii, 303–309.

(7) Schridde, H.: Über die Epithelproliferationen in der embrionalen menschlichen Speiseröhre. *Virchow's Arch.*, 1908, cxci, 179–192.

(8) Buchanan, George: Malformation of duodenum in a child. *Trans Path. Soc. London*, 1861, xii, 121–129.

(9) Ochsner, A. J.: Constriction of the duodenum below the entrance of the common duct and its relation to disease. *Ann. of Surgery*, 1906, xlii, 80–87.

(10) Finney, John M. T.: The relation of dilatation of the duodenum to gastric disturbances. *Johns Hopkins Hosp. Bull.*, 1906, xvii, 37.

(11) Bloodgood, Joseph C.: Acute dilatation of the stomach—gastromesenteric ileus. *Ann. of Surgery*, 1907, xlvi, 736–762.

(12) Bloodgood, Joseph C.: Dilatation of the duodenum in relation to surgery of the stomach and colon. *Jour. Am. Med. Assn.*, 1912, **59**: 117–121.

(13) Moore, Norman: Multiple diverticula of the small intestine with congenital stricture of the duodenum. *Tr. Path. Soc.*, London, 1884, xxxv, 202–204.

(14) Silcock, A. Q.: Epithelioma of ascending colon; enterocolitis; congenital duodenal septum with internal diverticulum. *Tr. Path. Soc.*, London, 1885, xxxvi, 207.

(15) Keith, A.: Constrictions and occlusions of the alimentary tract, of congenital or obscure origin. *Brit. Med. Jour.*, 1910, i, 301–304.

(16) Wilkie, D. P. D.: Duodenal diverticula and duplicature of the duodenal wall. *Edinburgh Med. Journ.*, 1913, xi, 219–229.

(17) Terry, W. J., and Kilgore, A. R.: Congenital stenosis of the duodenum in an adult. *Jour. Am. Med. Assn.*, 1916, **66**: 1774–1776.

(18) Nagel, Gunther, W.: Unusual conditions in the duodenum and their significance. *Arch. Surg.*, 1925, xi, 529–549.

Congenital Cysts of the Lung

By Amos R. Koontz

From the Department of Pathology of the Johns Hopkins Hospital and University

THE condition of congenital cystic lung represents a rather rare type of congenital anomaly. All the cases which could be found in the literature have been tabulated in this paper (Table I). The total number is 108. However, in order to make the list comprehensive, several cases of allied conditions, such as diverticula of the trachea or main bronchi, solitary cysts of the tracheal or bronchial wall, cysts of aberrant lung tissue and of accessory lobes, have been included. The total number of cases similar to the one here reported is considerably less than a hundred. Nearly all of them have been reported by the Germans, a few by the English, French and Italians. No American cases were found in the literature.[1]

Our case was that of an infant male white child delivered at the Church Home and Infirmary on June 24, 1924, by Dr. John G. Murray, Jr., and cared for by Dr. Murray and Dr. James B. Holmes until its death, twelve days later. Both parents were normal individuals from the higher walks of life. This was their first child. The autopsy protocol (No. 6630) follows:

[1] Dr. Robert T. Miller, Associate Professor of Surgery in the Johns Hopkins Medical School tells me that he has had a clinical case of this condition, a report of which will soon be published.

Anatomical diagnosis. Multiple congenital cysts of the lung. Cardiac hypertrophy and dilatation; chronic passive congestion of the liver; bloody effusions into pleural, pericardial and peritoneal sacs; Rammstedt operation for pylorospasm.

Clinical history. Child delivered by difficult mid-forceps operation because of dystocia due to uterine inertia. Extraction difficult, although the mother's pelvis was normal; this difficulty being due to the extreme hardness of the child's head and its rather large size. Weight at birth eight pounds and nine ounces. Diameters of head at birth: Biparietal 10 cm., occipito-frontal 13 cm., and suboccipito-bregmatic 10.25 cm. Child asphyxiated at birth but resuscitated with some difficulty. There were deep facial abrasions due to the forceps.

The baby presented no abnormal signs until June 29, its fifth day, when it was noticed that it was not regaining its birth-weight in spite of forced water, and supplemental feedings of cow's milk mixtures, in addition to nursing. On this day there was also a temperature of 101°, supposedly due to inanition. The following day the temperature was 103° and the child was still losing weight, in spite of forced feedings as before. The stools, although milk had been taken for three days, showed no milk residue. On this day thorough examination of the head showed that the sutures were not wider than before and that the child was normal in every respect. The following day, July 1, the seventh day of life, it was noticed that the child was having infrequent twitchings of the left supra-orbital muscles, followed by twitchings of the right hand, and these succeeded by more or less generalized convulsive movements of the legs. At this time it was also noted

that the sutures seemed to be wider than before. In spite of the ingestion of food the stools still retained the meconium character. Although there was little change in weight, the temperature was lower. During the night it was noticed that the child was less eager to nurse than before, and that it frequently had difficulty in breathing. The following day there was a slight gain in weight but the stools still showed no milk residue. There was no elevation of temperature. The sutures showed little, if any, change from their condition on the day before and the fontanel was not bulging. On the morning of the ninth day the child had gained a good deal in weight; its temperature was essentially normal and its general condition seemed excellent. A few hours after this examination, however, just after being fed, there was a sudden respiratory failure with extreme cyanosis. Examination showed the sutures possibly a little wider, and the fontanel full, although not bulging. A lumbar puncture was done and with some difficulty two drops of clear fluid were obtained. A decompression was considered, but abandoned, as the child was thought to be *in extremis*. The baby rallied, however, and some six hours later was in good condition and took its feedings well. During this day extreme abdominal distention appeared and as the bowel movements still contained no milk residue, it was felt, although flatus had been passed, that there might be some congenital obstruction in the gastro-intestinal tract. A thorough examination showed no palpable abdominal mass and a rectal tube was passed for some four inches and a stomach tube for an equal distance. No fecal matter was found in the rectal tube and only a few bubbles of gas from the stomach. In spite of nurses' observations that the child had vomited, repeated efforts to induce vomiting had caused no results. Once on this day, however, about 8 p.m. the baby vomited, in projectile fashion, about a teaspoonful of milk. During the night there were frequent slight attacks of respiratory failure. On the next day, the tenth, it was noticed that the abdominal distention was slightly more pronounced. Again, a thorough examination showed no gross abnormality of the abdominal organs and there was no obstruction to the passage of the catheter as rectal and stomach tube. Examination of the heart showed that a systolic murmur, which had occasionally been heard before, was present. Shortly after this examination a definite gastric peristalsis from left to right was noticed in the region of the distended stomach, and in view of this fact and the slight clinical evidence of a possible obstruction, an exploratory laparotomy was done. It was felt that there was some evidence of a pyloric stenosis, so a typical Rammstedt operation was done. Examination of as much of the intestinal tract as possible was made, and no abnormality noticed. The baby stood the operation well, although about an ounce of ether was administered. Some two hours after the operation, however, shock signs appeared, and stimulation was necessary. The following day, July 5, the eleventh day of life, the child showed little, if any, change. Castor oil was administered and some two hours later the first fecal stool obtained. The general condition of the child did not improve, however, and there was frequently difficulty in breathing requiring artificial respiration. The following morning signs of increased intracranial pressure again were more pronounced and again a decompression operation was considered, but abandoned. During the day the respiratory attacks became more frequent and longer, and the use of stimulants became more necessary. At 9 p.m. there was an extremely severe attack from which the baby recovered, but the next, occurring at 11:30 p.m. proved fatal.

Clinical diagnosis. 1. Birth injury to intracranial contents, probably with intracranial hemorrhage, following forceps.

2. Congenital pyloric stenosis. Operation.

Gross Findings. Body: Weight—4 kilos. Length—57 cm. Nutrition—good. Maceration—none.

Skin. The entire surface is mottled with purplish-red discoloration. There is a fresh midline surgical incision on the abdomen extending from the epigastrium to a point one half inch below the umbilical cord. The latter is dried and blackened.

Head: Size—normal. Shape—normal.

TABLE I

Collected cases

CASE NUMBER	YEAR	AUTHOR	SEX	AGE	SIDE	CLINICAL NOTE	CAUSE OF DEATH	PATHOLOGY	REMARKS
1		Fontanus		3 months	Both	Cyanosis		Lungs partly replaced by a bladder of air, communicating with the bronchi	
2		Valisneri			Both			Lungs partly replaced by a bladder of air connected with the bronchi	
3		Nonnus	♀	3 years	Both		Quartan fever	Both lungs consist of a sac of pus	
4		Gairdner	♂	66 years	L			Bronchiectatic cavities in left lower lobe, devoid of pigment	
5		Rokitansky	♂	Stillborn	L			Left upper lobe contained a cystic tumor size of a goose's egg	
6		Virchow	♂	9 months	Both			Both lungs cystic	Cretin
7		Winslow			Both			Lungs partly replaced by a bladder of air communicating with the bronchi	
8	1687	Bartholinus	♂	4 years	L		Marasmus	Upper lobe of left lung consisted of a sac of air	
9	1816	Rokitansky	♂	8 days	L	Cyanosis		Cystic tumor, size of citron, in left upper lobe	Heart displaced to right
10	1819	Köstlin	♀	22 years	L	Bronchitis 4–12 years	Peritonitis	Left lung small, hard, bluish, without air. Bronchi enlarged, contained mucus, no alveolar epithelium	Right lung very voluminous
11	1858	Kessler	♀	1 year	L	Wheezing, cyanosis, irregular heart action for 7 months		Left lung in 2 parts, the upper, a large fibrous sac filled with air, the lower consisting of 3 small lobes	
12	1859	Meyer		6 months fetus	Both			Cyst size of hazel-nut at right hilus communicating with bronchus, small cysts over surface of both lungs	
13	1860	Biermer	♂	33 years	R			Right lung very small, consisting of a series of canals ending in sacs	
14	1860	Biermer			L			Left lung small, lobes adherent, upper lobe consists of multilocular bronchiectatic cavities	
15	1860	Tillaux	♀	35 years			Peritonitis	Circumscribed multilocular cystic tumor of pleura, size of two fists	
16	1861	Roktoržik	♀	14 days	L		Peritonitis	Small lobe not connected with lung containing branching canaliculi and incompletely formed alveoli	

17	1861	Rokitansky	♀	3 months	L			Accessory lobe attached to left lower lobe; no bronchus	
18	1877	Lesser	♀	4½ months	Both		Broncho-pneumonia	Cysts size of cherry-stone over surfaces of both lungs, not communicating with bronchi	
19	1878	Froentzel	♂	25 years	R	Cough from infancy, cyanosis	Pneumo-thorax	Right lung cystic; cysts varying from size of pea to a large sac; contain reddish fluid	Left lung emphysematous. Heart displaced to left
20	1880	Grawitz	♀	Stillborn	R	Made some vain efforts to breathe		Right lower lobe size of a hen's egg; a multilocular sac filled with fluid; no communication with bronchi	Left lung and right upper and middle lobes atelectatic. Heart increased in size. Foramen ovale open. Hemorrhage on face and head
21	1880	Grawitz	♂	38 years	R	Marked dyspnea, cyanosis and cough		Right lung size of two fists, and consists of 2 cystic lobes; cysts size of hasel-nut to pigeon's egg; communicate with bronchi; no pigment in cystic lobe	Left lung voluminous
22	1880	Barlow		3 months	L	Cough, without dyspnea		Congenital atelectasis and emphysema. Left upper lobe contains a cyst, size of a chestnut	
23	1883	Coats	♂	46 years	L	Dyspnea and venous stasis, in last month of life only		Left lung small, especially upper lobe, which consists of connective tissue and dilated bronchi	Compensatory hypertrophy of right lung
24	1883	Feustell	♀	7½ years	R		Scarlet fever	Right lower lobe small—no pulmonary tissue—irregular cavities up to 8 mm. in diameter; cartilage well developed	
25	1883	Recklinghausen	♂	40 years	L			Left lung atrophied—half size of a fist. Atelectatic with bronchial dilatations	Right lung hypertrophied
26	1883	Chiari	♀	68 years	Both		Emphysema	Saccular and cylindrical dilations of bronchi of both lower lobes. One mixed tumor of a bronchial wall, size of a pea	
27	1883	Hamilton						Cavities ¼ to ½ in. in diameter with smooth walls	Bronchitis of smaller bronchi:
28	1885	Schlicht	♀		L		Pneumonia	Left lung very small with bronchiectasis	Right long hypertrophied
29	1885	Frühwald	♀	5 months	L	Cyanosis and cough		Part of left lung cystic	
30	1885	Heller		9 months			Pneumonia	Part of lung showed atelectatic bronchiectasis	
31	1885	Heller		6½ years	L		Scarlet fever	Left lower lobe showed atelectatic bronchiectasis	
32	1885	Heller		7½ years	R		Scarlet fever	Right lower lobe showed atelectatic bronchiectasis	

TABLE I—*Continued*

CASE NUMBER	YEAR	AUTHOR	SEX	AGE	SIDE	CLINICAL NOTE	CAUSE OF DEATH	PATHOLOGY	REMARKS
33	1886	Balzer and Grandhomme	♀	15 minutes	L			Left upper lobe cystic	No connection between cysts
34	1886	Braun	♂	11 years	L			Atelectatic bronchiectasis of left lung	
35	1887	Herxheimer		48 years	R			Part of right upper lobe showed atelectatic bronchiectasis	
36	1887	Herxheimer		65 years	R			Right lung showed atelectatic bronchiectasis	
37	1887	Herxheimer		49 years	L			Left lung showed atelectatic bronchiectasis	
38	1888	Stilling	♂	45 years			Cerebral hemorrhage	Cystic tumor, size of egg, in anterior mediastinum lined with ciliated columnar epithelium and having cartilage in the wall	
39	1889	Chiari						Congenital diverticulum of trachea	
40	1890	Chiari			R			Congenital diverticulum of right main bronchus	
41	1891	Wollmann	♀	24 years	L	Cough from infancy. Dyspnea, abundant expectoration, signs of cavities, cyanosis		Left lung very small, consisting of bronchial dilatations and atelectatic lung tissue	Right lung very large. Heart displaced to left
42	1891	Sottas	♂	53 years	R	Signs of tbc. at rt. apex, no tubercle bacilli	Pneumonia, left	Right upper lobe a sponge of cavities of various sizes	Excessive development of smooth muscle
43	1891	Berlin	♀	52 years	R		Cancer of sigmoid flexure	Atelectatic bronchiectasis lower half of right upper lobe. No pigment. Cysts pea-size to size of hazelnut	Acquired bronchiectasis, upper half of same lobe
44	1892	Sharkey	♀	2 years	Both	Diptheria 10 days before death, followed by pneumonia	Pneumonia	Acute peribronchitis, extreme bronchiectasis, interstitial pneumonia	
45	1892	Sharkey	♂	4 years	Both	Cough and expectoration 2 months. Terminal pneumonia	Pneumonia	Smooth-walled cavities up to the size of a pea through out both lungs	Subcutaneous emphysema of body and arms
46	1894	Francke	♂	58 years	Both	Cough and sputum since age of 20. Signs of chronic bronchitis and emphysema		Left lung size of a fist—bronchi large, terminating in saccular dilatations. Parts of right upper and lower lobes likewise affected	
47	1895	Dürck	♀	9 months	R	Rickets and bronchitis	Broncho-pneumonia	Accessory lobe in angle between right posterior thoracic wall and diaphragm. Bronchus ending blindly	

48	1896	Zahn	♀	32 years	L		Chronic phthisis	Cystic tumor size of hen's egg in visceral pleura lined with ciliated columnar epithelium and with cartilage in the wall	
49	1897	Stoerk	♂	Newborn	R			Cystic right middle lobe—very large	Also ascites and bilateral hydrothorax
50	1897	Tooth	♂	18 months	Both	Cough, labored respirations and signs of general bronchitis 11 days	Pneumonia	Both lungs full of cavities from size of millet seed to size of almond; not connected with bronchi	
51	1897	Fisher	♂	5 years	Both	Several attacks of bronchitis; terminal pneumonia	Pneumonia	Entire right lung and part of left upper lobe riddled with cavities up to ½ inch in diameter, and full of pus	Pneumonia of regions containing cavities. Rest of lung normal
52	1897	Rohmer-Borchert	♀	Young	L		Meningitis	Left lung small (12 x 7 cm.) and cystic, due to occlusion of main bronchus	
53	1897	Stoerk	♂	44 years	R			Cystic accessory lobe attached to right upper lobe	Cysts not communicating with bronchi
54	1897	Rindfleisch	♂	40 years	Both	Steadily increasing breathing difficulties	Heart failure (?)	Cysts in both lungs throughout, from pinhead size to size of pigeon's egg	
55	1898	Arnheim	♀	2½ years	Both	Breathing difficulties. Rickets		Both lungs contain honeycomb-like bronchial widenings	Total right-sided body hypertrophy
56	1898	Virchow-Heubner	♂	3 years	L	Chronic bronchiectasis for two years	Miliary tbc. following measles	Bronchiectasis of left lower lobe	Authors unable to account for it unless it was congenital
57	1898	Springer	♀	48 years	L		Heart failure (?)	Small cystic accessory lung attached to left lower mediastinal pleura	
58	1899	Bard	♂	30 years	L	Dyspnea and cough from infancy. Last 6 months marked cyanosis and fetid expectoration		Left lung full of bronchial dilatations varying in size from that of a pea to that of an orange, walls inflamed and suppurating	Right lung hypertrophied. Heart dilated and hypertrophied
59	1899	Linser	♂	13 years	L	Cough with increasing evidence of tumor in left thorax		Congenital cystic tumor of left lung: cavities surrounded by cartilage	Sarcomatous degeneration
60	1899	Paul	♀	55 years	L			Atelectatic bronchiectasis of left lower lobe	
61	1899	Vogel	♂	47 years	L		Cancer of the stomach	Flat plate-like mass of cystic lung tissue under left diaphragm	
62	1899	Vogel	♀	28 years	L		General tuberculosis	Walnut-sized tumor under left diaphragm composed of cystic lung tissue	
63	1900	Thomas	♀	60 years	R	Winter cough. Dyspnea. Abundant expectoration	Broncho-pneumonia	Multilocular cavity in right apex communicating with a bronchus. Bronchi dilated elsewhere in places. Vessels accompanying bronchi very large	Left lung emphysematous. Generalized bronchitis. Bronchopneumonia and edema at bases. Heart dilated

TABLE I—*Continued*

CASE NUMBER	YEAR	AUTHOR	SEX	AGE	SIDE	CLINICAL NOTE	CAUSE OF DEATH	PATHOLOGY	REMARKS
64	1900	Wechsberg		Newborn	L			Tumor of left lung with pedicle from posterior mediastinum near oesaphagus, consisting of cysts lined with cuboidal and ciliated columnar epithelium	
65	1900	Delobel	♂	19 years		Cough for one year		Bronchiectasis of one lower lobe	
66	1901	Fletcher	♂	3½ years	Both	Attack of bronchitis at 4 months Cough and dyspnea 3 weeks before death		Lungs riddled with cavities from pin-head size to size of a pea	Cholangitis with cystic dilatation of bile-ducts
67	1902	Busse	♀	58 years	L	Pulmonary congestion complicating hemorrhagic nephritis		Only a stump of left lung; this contained dilated bronchi. Increase in elastic tissue	Right lung markedly hypertrophied
68	1902	Lyonnet	♀	25 years	Both	Cough, expectoration, dyspnea and cyanosis of 5 or 6 years' duration		Numerous bronchial dilations of both lungs size of small almonds, filled with purulent fluid	Right heart dilated. Foramen ovale patent
69	1903	Humbert	♀	63 years	L	Dyspnea for several years. Expectoration abundant. No tubercle bacilli. Cyanosis		Left lung condensed, size of a normal kidney, full of cavities (dilated bronchi) ranging in size from that of a nut to that of a mandarin.	Right lung very voluminous
70	1903	Dionisi						Congenital polycystic lung degeneration	
71	1903	Dionisi						Congenital polycystic lung degeneration	
72	1903	Lewisohn		4 months	L		Cerebrospinal meningitis	Cystic accessory lobe attached in under surface of left lower lobe by a small pedicle	
73	1904	Couvelaire		6 days	R	Respiratory difficulty for one day		Right middle lobe consists of cyst-adenomatous malformations	
74	1904	Humbert	♂	25 years	L	Never good health. Cough from age of 8. Blood-streaked expectoration at 19 or 20. Purulent fetid sputum		Left lung like a sponge, with the largest meshes the size of a bird's egg. All cavities red, inflamed, with adherent exudate	Area of gangrene size of a small nut in center of right lower lobe, surrounded by an area of broncho-pneumonia
75	1904	Humbert			L	Grave respiratory difficulty	Capillary bronchitis	Dilated bronchi of left upper lobe with aplasia of parenchyma	Mitral lesion
76	1904	Humbert	♂	65 years	Both	Cough and expectoration all life. Dyspnea and cyanosis		Dilated bronchi extending to periphery of lung on left; much fibrosis of surrounding parenchyma. Vessels accompanying dilated bronchi very large	
77	1904	Kaufmann			L			Large branching cavities of left lung	

78	1904	Kaufmann			L			Left lung voluminous consisting of large sponge-like tissue	
79	1904	Handó		Stillborn				Large cavities in lungs	
80	1904	Edens	♂	22 years	Both	Cough, sputum, dyspnea, and cyanosis		Cysts of both lungs and widened bronchi. Left lower lobe atelectatic and pigment-free	Pleuritic adhesions. Cysts lined with ciliated xolumnar epithelium
81	1904	Muus	♂	1 day	L	Cyanosis		Polyp size of a walnut consisting of cystic aberrant lung tissue under left lower lobe: no communication with bronchi	
82	1904	Hammar	♂	fetus	L			Two small cysts of left bronchi but not communicating with them	
83	1905	Bernstein	♀	3 years	Both	Pain in back for 3 months: cough one month; pneumonia and right pneumothorax 3 days	Pneumonia	Both lungs full of smooth-walled cavities from pin-head size to ½ inch in diameter Lined with columnar epithelium	Giant cells in walls of cavities. No tuberculosis
84	1905	Orth	♂	44 years	L		Acute pancreatitis	Left lung smaller than normal, without pigment, and covered with hazel-nut-sized blebs	Right lung tissue normal, lung larger than normal
85	1905	Orth		4 years	Both		Pneumonia	Both lungs full of pea-sized cysts	
86	1905	Beneke	♀	Newborn	L			Large accessory lung with bronchus ending blindly at stomach wall	Left sided diaphragmatic hernia
87	1905	Seltsam	♂	9 weeks	L		Pneumonia and enteritis	Hazel-nut-sized cystic lung lying close under left posterior diaphragm	
88	1906	Pepere	♀	16 years	Both	Chronic bronchitis		Multiple cysts of both lungs up to 1.5 cm. in diameter	
89	1907	Sandos	♀	17 years	Both	Increasing dyspnea, cyanosis and cardiac insufficiency	Pneumonia	Small cavities and emphysematous blebs throughout both lungs	These patients were twins sisters
90	1907	Sandos	♀	18 years	Both	Increasing dyspnea, cyanosis and cardiac insufficiency		Small cavities and emphysematous blebs throughout both lungs	
91	1907	Zipkin	♀	Stillborn	Both			Large cystic left lung containing a rhabdomyoma. Aplasia of right lung	Several congenital heart defects
92	1908	Lotmar	♀	50 years	L	Accidental finding at autopsy		Fetal atelectasis of left lower lobe, cavities formed from widened bronchi; no pigment	Pleura thick and adherent. No cartilage in walls of bronchi
93	1908	Lotmar	♂	50 years	R	Accidental finding at autopsy		Atelectatic bronchiectasis of right lower lobe with white lung stroma	
94	1911	Buchmann	♂	84 years	R		Apoplexy	Right upper and middle lobes contain cavities communicating with bronchi and containing muco-pus. Walls contain strongly developed muscle, elastic tissue and cartilage	No pigment in affected parts. Pleura thickened and adherent. Lung tissue not recognisable

TABLE I—*Continued*

CASE NUMBER	YEAR	AUTHOR	SEX	AGE	SIDE	CLINICAL NOTE	CAUSE OF DEATH	PATHOLOGY	REMARKS
95	1911	Buchmann	♂	49 years	Both	Chronic bronchitis with dullness in both upper lobes for many years. Terminal hemoptysis		Both upper lobes full of 0.5 to 4 cm. large cavities communicating with bronchi. Intervening tissue atelectatic and lacking in pigment. Adherent pleura	
96	1911	Buchmann	♂	55 years	R	Treated for many years for pulmonary tuberculosis. Hemoptysis at times		Congenital cysts of right upper and middle lobes communicating with bronchi. Intervening tissue atelectatic without pigment.	Lipoma of right lower lobe. Healed tuberculosis of left upper lobe and of adrenals.
97	1911	Buchmann	♂	51 years	R	Always weak. Cough and expectoration	Cancer of trachea	Right lower lobe small, 9 x 4 cm. Bronchi widened. Lung tissue atelectatic, lacking in pigment. Pleura thick and firmly adherent	
98	1911	Buchmann	♀	55 years	Both	Cough with mucous expectoration for a year. Dyspnea, cyanosis, anorexia	Pneumonia	All lobes contain cystic cavities communicating with bronchi, pleura adherent	Giant cells—No tuberculosis
99	1911	Bert and Fischer	♀	60 years	L		Fractured skull	Cystic accessory lung, 3 x 2 x 1.5 cm., between left lower lobe and diaphragm	
100	1914	Heuter	♀	69 years	L			Left lower lobe contained many pea-sized cavities, filled with pus—Alveoli not developed	
101	1914	Heuter	♀	Stillborn	L			Left lower lobe contained many pea-sized cavities. Resembled a sponge	
102	1921	Gold	♂	8 months	L	Cough, dyspnea, tympany, râles		Solitary cyst to right of bifurcation of trachea, contains mucus. No connection with bronchus	
103	1921	Gold	♀	½ hour	R	Accidental autopsy finding		Several cysts lying behind right main bronchus. No communication with bronchus	
104	1921	Gold	♂	3½ months	R	Accidental autopsy finding		Single cyst behind right main bronchus	
105	1921	Gold	♀	3½ years	R	Accidental autopsy finding		Single cyst by right main bronchus	
106	1924	Oudendal	♂	30 years	R	Found dead on roadside	Pneumonia	Right lower lobe entirely cystic. Cysts 0.5 to 4½ cm. in diameter containing muco-pus	
107	1924	Oudendal	♂	32 years	R		Fractured skull	Right lower lobe consists of a system of cavities with smooth walls	Old adhesions between affected lobe and thoracic wall
108	1924	Oudendal	♀	40 years	L			Numerous cavities of left lower lobe containing muco-pus and communicating with bronchi	Numerous miliary tubercles of both lungs

Eyes—the pupils are unequal, the right being slightly larger than the left. They are regular and not dilated. Nose—there is a copious sero-sanguineous discharge.

Thorax: The thorax is well formed. There are no thickenings of the costochondral junctions. The thymus is normal. The mediastinal glands are not enlarged. Each pleural cavity contains from 30 to 50 cc. of blood-stained fluid. There are about 20 cc. of blood-stained fluid in the pericardial sac.

Abdomen: The abdomen is distended. The peritoneal cavity contains considerable fluid (about 100 cc.) which is slightly blood-stained. The intestines are markedly distended with gas.

Peritoneal, pleural and pericardial sacs: Surfaces—smooth and glistening. Adhesions—between transverse colon and pylorus. Position of viscera—normal. Retroperitoneal and mesenteric glands—not enlarged.

Thymus: Normal.

Heart: Weight—50 grams. Lesions—the blood vessels of the epicardium are markedly dilated. The myocardium is hypertrophied. The heart is very large; all the valves are delicate and competent. There are no congenital anomalies. There is a chicken-fat clot in the right auricle.

Lungs: Air crepitus is present and the lungs float in water. There are a goodly number of cystic and emphysematous blebs present over the surface of both lungs. On section (Fig. 1) numerous cysts are found throughout both lungs, varying in size from those barely visible to those 3 mm. in diameter. Marked congestion throughout. In the right upper lobe there is a patch of red consolidation 2 cm. in diameter.

Spleen and Pancreas: Normal.

Stomach and duodenum: There is a longitudinal surgical incision 1 cm. long in the pyloric sphincter dividing the muscle coats. The pylorus is not hypertrophied. The mucous membrane of the duodenum is intensely hemorrhagic. There are scattered hemorrhagic spots in the mucosa of the stomach, especially along the greater curvature. The bile-ducts are patent.

Liver: Weight—220 grams. Lesions—chronic passive congestion.

Adrenals: Normal.

Kidneys: Weight—20 grams. Lesions—congestion.

Pelvic organs: There is a small hemorrhage in the mucosa of the bladder near the vesical orifice; otherwise, normal.

Intestines: The mucosa of the transverse colon is hemorrhagic in spots. The mucosa of the rectum and sigmoid is markedly congested.

Aorta: Normal.

Bones: Not examined.

Skull and dura: Normal.

Brain: All the surface vessels are markedly congested. There is no hemorrhage

FIG. 1. GROSS APPEARANCE OF THE CUT SURFACE OF A LOBE OF THE LUNG

on the brain surface. The brain on section shows no hemorrhage or other obvious abnormality.

Microscopical notes. Lung: The lungs present a most remarkable picture. One is at once struck by the large number of cysts of various sizes. The lung tissue between the cysts is mostly atelectatic. There are very few inflated areas and these are principally at the periphery. On this picture is superimposed a condition of extreme infection which tends to obliterate structural details. Here and there abscesses are found and large clumps of bacteria. A bacterial

FIG. 2. POINT OF COMMUNICATION BETWEEN A BRONCHIOLE AND A CYST

The mucous membrane is shown thrown into folds, and the opening further obstructed by the presence of desquamated epithelium.

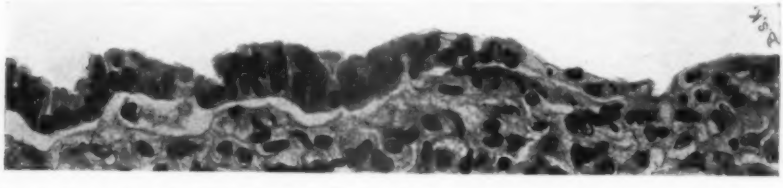

FIG. 3. ENLARGED DRAWING OF A PORTION OF FIG. 2, SHOWING THE GRADUAL TRANSITION OF THE COLUMNAR EPITHELIUM OF THE BRONCHIOLE INTO THE FLATTENED OUT EPITHELIUM OF THE CYST

stain (MacCallum's modification of Goodpasture's method) shows the organisms to be Gram-positive cocci. The area of red consolidation spoken of in the gross description is an area of extensive hemorrhage. There is considerable edema throughout, where the alveoli are not collapsed. In some places heart-failure cells are numerous. There is considerable increase in interlobular connective tissue. In various places there are collections of lymphoid elements.

The cysts are numerous and of different sizes, varying from the size of a normal alveolus to 3 mm. in diameter. They communicate freely with each other, as shown by a study of serial sections, but do not communicate with the alveoli. They are lined with very much flattened out epithelial cells where the lining still persists, but in most places the lining epithelium has disappeared, leaving the basement membrane exposed. They are partially filled with edema fluid. The bronchi and bronchioles are diminished in number. Several places where bronchioles communicate with cysts are found in a series of 50 serial sections. One of these is shown in Fig. 2. There is a gradual transition from the stratified columnar epithelium lining the bronchioles to the flat epithelial cells lining the cysts (Fig. 3). There is an excessive development of the cartilage of the larger bronchi. About these bronchi the muscle and elastic tissues are very poorly developed, while there is none at all around the smaller ones. There is a slight connective-tissue support which thins out at the cysts. (Verhoeff's elastic tissue stain and van Gieson's connective-tissue stain were used in making these studies). A constriction is to be noted at the point of communication between bronchiole and cyst (see Fig. 2), due partly to the mucous membrane being thrown into folds at this point and partly to the collection of desquamated epithelial cells and debris from other areas.

Spleen: Normal.

Heart: The heart muscle shows marked hypertrophy.

Adrenal: The capillaries are widely dilated and filled with blood. In many places the blood has extravasated from the capillary bed. This condition is most marked in the medulla, but is also present in the cortex.

Kidneys: There is cloudy swelling of the epithelium of the convoluted tubules.

Liver: The sinuses are full of blood. There is marked fatty change in the liver cells except immediately around the portal spaces.

Pancreas: There is an increase in connective tissue.

Duodenum: The vessels of the submucous coat are engorged with blood. The distal portion of the mucosa shows varying depths of necrosis, in some places reaching down to the fundi of the glands.

Thymus: There is a marked increase in fibrous tissue. The cortex and medulla are not well differentiated. The lymphocytes are greatly reduced in number and collected around the Hassall's corpuscles. The predominating type of cell is one that somewhat resembles the normal medullary cell, but is larger and contains a large vesicular nucleus. The vessels are engorged.

The foregoing description of the microscopical structure of the lungs indicates that the cause of the cysts in this case was a constriction of the walls of the bronchioles with a dilatation of the parts distal to it. The cause of the excessive development of the mucous membrane, which forms the constrictions in the bronchioles, is a matter not quite so easily disposed of. It involves the question of the underlying cause for the entire condition. Many different opinions have been expressed and these will be discussed later. However, these conjectures serve only to becloud the issue. It seems useless to attempt a simple mechanical explanation for a condition which is evidently a developmental anomaly, and in the formation of which many unknown factors must be concerned.

The terminology in the literature is rather confusing. The following terms are encountered and are used synonymously: fetal bronchiectasis, congenital cyst formation of the lung, congenital cystic malformation of the lung, atelectatic bronchiectasis, congenital bronchiectasis, honeycomb lung, and others. Grawitz uses the term "congenital bronchiectasis" and makes two subdivisions, as follows: universal bronchiectasis, in which a whole bronchus is dilated; and teleangiectatic bronchiectasis, in which bronchial cysts are formed. The multiplicity of terms is due to the different

TABLE II

	SEX			SIDE AFFECTED			
	Male	Female	Not mentioned	Right	Left	Both	Not mentioned
Congenital cysts	42	41	25	26	46	27	9
Hypoplasia	8	5	5	6	11	0	1
Aplasia	5	3	8	8	7	1	0

interpretations, by the various authors, of the nature and origin of the lesion.

The age at which these cases are found at autopsy covers the entire span of human life, extending from premature still-births to extreme old age. In the patients who have reached maturity, it would often be difficult to determine whether the lesion was congenital or acquired, were it not for the total lack of pigment in the congenital lesions, showing that the affected part of the lung had never functioned, and that therefore the pathological condition antedated birth. These pigment-free portions of lungs containing congenital defects are often sharply contrasted with adjacent portions exhibiting acquired pathological lesions of a similar nature, but which are deeply pigmented.

The incidence, as to sex, and the side on which the lesion occurs, is given in Table II. It will be seen that males and females are affected equally often. In one-fourth of the cases both lungs were implicated, in another fourth only the right lung contained cysts, while in nearly half only the left lung was involved.

As would be expected, this condition is not confined to man, but is also found in animals. Glur has shown that, in cattle, one of the lobes of the lungs is occasionally rudimentary, while the others are normal. The rudimentary lobes are accidental autopsy findings without any history of illness, and have the character of bronchiectasis and lung cysts. Glur cites three cases of his own and mentions two of Reisinger's.

Other developmental defects of the organs derived from the primitive foregut are encountered fairly often. Ruge and others describe pinched-off bits of lung tissue that are in no way connected with the lungs proper. In Ruge's case a small third lung, which lay under the left lung but was in no way connected with it, received a vessel from the seventh left intercostal space. In the case of Muus, the pinching-off effect had caused the formation of a polyp of cystic, aberrant lung tissue, which had no connection with the cavities of the lung. Other cases of supernumerary or accessory lungs are recorded (Allen, Beneke, Chiene, Cleland, Collins, Edwards, Handford, Herxheimer, Humphry, Loewy, Pozzi, Quenzel, Schaffner, Seltsam, Voisin and others), some occur-

ring in the thoracic and some in the abdominal cavity.

Cysts of the esophagus, liver and mediastinum lined with ciliated columnar epithelium have been reported by several authors (Coesfeld, Eberth, Friedreich, Herrmann, Joël, Kern, Kraus, Mohr, Rau, Recklinghausen, Ribbert, Stilling, Trespe, Virchow, von Wyss, Zahn and others), showing that pinched off inclusions from the developing respiratory tract are varied in form.

Chiari and Kahler have reported a number of cases of diverticula of the trachea and main bronchi.

Abnormal lobation of the lung is far more common, and occurs most often on the right side. There may be an increase in the number of fissures, giving rise to extra lobes; or a fissure may be lacking, causing a combination of two lobes.

In many of the reported cases of congenital cystic lung there was a history of grave respiratory difficulties from birth. In others, in which the extent of the lesion was considerable, there was no such history and the condition was recognized only at autopsy. Many of the patients presented the clinical picture of chronic phthisis but without tubercle bacilli in the sputum.

STRUCTURE

It will be seen, at a glance at Table I, that all the cases of congenital cysts of the lung have many points in common as regards structure. However, a closer study of the literature from which the table is compiled shows that there are considerable differences in detail.

There are in general two types of cavities: (*a*) bronchial dilatations, as shown by the concentric muscle fibers in the walls, cartilage at times, and the lining of stratified ciliated columnar epithelium; and (*b*) cavities resembling emphysematous blebs lying subpleurally. There are all sorts of variations and gradations of these two, as well as transition types. These cavities vary greatly in size and distribution. In many cases no communication can be traced between the cysts and the bronchi, while in other cases careful serial sections show that such a communication exists.

While in most cases the cavities are lined with ciliated columnar epithelium in which there is generally a tendency to layering, epithelium of various sorts is found—cuboidal, cylindrical, with or without cilia, one or more layers, flattened out cells, or none at all, denuded connective tissue forming the lining wall. Small and medium-sized cavities are principally lined with many-layered ciliated columnar epithelium, while the larger cavities have flat to cuboidal cells. There is generally a distinct membrane propria on which the lining epithelium rests, and in cases in which the epithelium is desquamated the membrana propria forms a smooth wall for the cavity.

External to the mucous membrane are generally found elastic tissue, white fibrous tissue, concentric fibers of smooth muscle, and pieces of cartilage. The arrangement of these tissues is varied, and there is often an excess of elastic tissue and smooth muscle, the latter frequently appearing in tumor-like masses. The cartilage is often clumped in irregular masses, and is not present as constantly as the other

tissues of the wall. Mucous glands are present in a moderate number of cases.

In many cases the mucous membrane is swollen and inflamed. Sometimes a marked lymphocytic reaction is present. Retention cysts, formed from the mucous glands, are encountered. Granulation tissue is sometimes present, and in two cases (Buchmann, Bernstein) it contained foreign-body giant cells, and giant cells of the Langhans types. In neither case was there any trace of tuberculosis. Indeed, an associated tuberculosis is recorded in only five of the total number of reported cases.

The lumen of the cavities generally contains clear fluid, which is often high in albumin content. At times the cavities are empty. Desquamated epithelial cells, lymphocytes, pus, or mucus are found in different cases.

NATURE OF THE LESION

Much has been written as to the nature and cause of these lesions, but there is no general agreement with regard to them. The following are some of the views held by different authors:

Grawitz believes the "hydropic cystic malformation" to be due to faulty *Anlagen* of the lymph-vessel systems of the corresponding lobes of the lung.

Stoerk believes that these abnormalities fall into two groups, (*a*) those cystic malformations due to fetal bronchiectasis secondary to inflammatory processs, with stenosis and closure of bronchioles in the fetus, and consequent cystic malformations through retention of secretions; (*b*) those cystic malformations due to excessive growth of the parts surrounding the bronchial tree, especially connective tissue, with retention of fetal characters.

Sandoz attributes the condition to faulty development of the alveoli from the small end-bulbs of the bronchial tree in the embryo. He holds that this faulty development is the result of congenital syphilis.

Kimla thinks that the condition is due to excessive growth of the mesodermic structures, with consequent parcelling out of the glandular structures, which then undergo cyst-adenomatous change.

Couvelaire believes that endoderm is the essential factor necessary and sufficient for the formation of cysts.

Buchmann thinks the cases are in reality examples of tumor change, as shown by the strong development of smooth muscle and the epithelial proliferation.

Humbert assigns the following causes for pulmonary malformations:

1. A complete absence of the lung bud.
2. An intra-uterine inflammation
3. The persistence of a fetal state
4. Faulty development

In discussing the complete absence of the lung bud, he points out that the condition has been described principally by the older authors, who gave very meager anatomical details. In discussing intra-uterine inflammation, he refers to syphilis especially as the cause, and points out that Balzer and Grandhomme particularly insisted upon this as an etiological factor, but states that our information is not complete enough to justify definite conclusions. For unknown reasons a part of a lung at times retains the characters which it had *in utero*. Secondary

atrophy takes place. This differs from primary atrophy in the fact that the bronchi and vessels have a normal distribution and structure. Faulty development is a most important factor, and explains a great variety of lesions. Besides the congenital bronchial malformations, generally admitted, Humbert thinks that there are cases forming a distinct morbid entity in which there are no malformations present at birth, but in which there is some defect in the structure of the bronchial walls, which later results in malformation.

According to Heuter, the cysts develop on account of a closing off or stenosis of bronchial branches. The earlier the process develops, the fewer and larger the cysts; the later, the more numerous and smaller, so that some lungs are honeycombed with them.

Heller considered the widened bronchi as due to respiratory pressure in lungs that were normal at birth, but failed to expand and remained in an atelectatic state.

Orth, Heller, Franke and others report cases of atelectatic bronchiectasis in which there was a lack of development of the alveoli, this being counterbalanced by widening of the bronchi. Heuter, also, reports a case which he considers as bronchiectasis due to aplasia of the alveoli.

Oudendal lays stress on the presence of a regular character of the cyst wall—lining epithelium, membrana propria, elastic fibers and muscle layers—as evidence of developmental anomaly rather than neoplasm. He lays special emphasis on the regularity of the elastic fibers. He also advances the theory (first mentioned, but never held, by Buchmann) that the cause of congenital cystic malformation of the lungs is probably fetal adhesions between the parietal and visceral pleurae, which bring about anomalous development. Fetal infection with lues is suggested as a possible cause of these adhesions.

British literature on this subject is very meager, and the cases are not thoroughly described. However, from what these authors have written and from the illustrations in their articles, there can be little question of the similarity of their cases to those described elsewhere. Yet, these observers do not seem to consider the condition as having a fetal origin. Box states that "the formation of a honeycomb lung is due to bronchopneumonia. Pleural adhesion plays no part in the initiation of the condition although it may develop later; for in many cases there is no pleural adhesion at all." Bernstein considers the condition due to the following sequence of events: Acute bronchitis and bronchiolitis, peribronchitis, broncho-pneumonia, ending in dilatation of the terminal bronchioles and infundibula. Tooth agrees with Bernstein as to the method of formation. Kanthack and Rolleston think the cysts are broken down abscess cavities but, nevertheless, describe them as having smooth and glistening walls. Microscopical details are lacking.

Klebs says that the defects of aplasia and hypoplasia are developmental mechanisms, and points out that most of such cases in the lung occur on the right side, whereas in the kidneys the arrest of development is generally on the left. He thinks that this is explained by the way in which the fetus

is usually curved *in utero*—with stretching of the left side and compression of the right.

From the foregoing, it is readily seen that there are many theories advanced as to the cause of the condition here considered. Each author who has reported cases has his own pet theory. The truth is probably to be found in a combination of the causes mentioned with the elimination of some of the more fantastic.

The relationship between the persistence of fetal atelectasis and the presence of atelectatic bronchiectasis is striking, and deserves further comment. Adami and Nicholls, in their *Principles of Pathology*, state that in atelectatic bronchiectasis "the dilated bronchi take the space that should be occupied by functioning air sacs," as a result of atrophy of their walls or of tension exerted by the contraction of interstitial fibrous tissue. They also state that the persistence of fetal atelectasis is due to several causes such as

> General asthenia or muscle weakness commonly present in immature children; weakness, owing to a syphilitic or other constitutional taint; lesions of the central nervous system, like cerebral hemorrhage or similar lesions of the brain; defects of development, such as hypoplasia of the lung and diaphragmatic hernia; finally, external causes, as compression of the thorax, obstruction of the bronchi by foreign bodies, meconium, or secretion.

To this may be added the following quotation from MacCallum:

> Since, in the adult, the thorax has grown to a size greater than could be filled by the collapsed lungs, there is even in the position of forced expiration a disproportion which keeps the lungs partly distended with air. In the infant, for a time, so nearly does the lung tissue fill the thorax, that the air which is found in the lung is quite proportioned to the respiratory movements. Atelectasis is, therefore, more easily produced or maintained in the infant than in the adult.

Sutherland believes that a congenital heart defect is a factor contributing to the persistence of fetal atelectasis:

> Another factor that plays a part in increasing the volume of the lungs after birth is the pulmonary circulation, and the new circulation through the lungs is also, in all probability, a stimulus to the respiratory centers. It has often been noticed in fatal cases of atelectasis that the fetal condition of the heart has persisted, the foramen ovale and the ductus arteriosus being still patent, and it has been assumed that this is a super-added defect in the infant. On the other hand, it may be that the persistent fetal condition of the heart has led to an imperfect pulmonary circulation, and has thus contributed directly to the non-expansion of the lungs.

This is interesting in view of the large number of congenital heart lesions encountered in cases of congenital cystic lung.

Holt and Howland state that where congenital atelectasis has persisted for some time, there are generally evidences of pneumonia found at autopsy. It is quite likely that, instead of pneumonia being the cause of honeycomb lung, as suggested by English authors, on the contrary, the presence of the cystic condition is a predisposing cause to pneumonia.

REFERENCES

(1) Adami, J. G., and Nicholls, A. G.: The principles of pathology, 1911, ii, 263 and 293.

(2) Allen, W.: A variety of pulmonary lobation and its relations to the thoracic parietes, as illustrated by comparative anatomy and abnormalities in the human subject. *Jour. Anat. and Physiol.*, London, 1882, xvi, 605–614.

(3) Appel, R.: Contribution a l'étude de la dilatation bronchique congénitale. *Thèse de Paris*, 1904.

(4) Armheim, G.: Über einen Fall von congenitaler halbseitiger Hypertrophie mit angeborenen Bronchiektasen. *Virch. Arch.*, 1898, cliv, 300–320.

(5) Balzer et Grandhomme: Contribution à l'étude de la bronchopneumonie syphilitique du foetus et du nouveau-né. *Rev. mens. des maladies de l'énfance*, nov. 1886. Quoted by Humbert and by Appel.

(6) Bard, L.: De l'existence d'un type périphérique de la form tardive de la maladie bleue. *Lyon méd.*, 1899. Quoted by Humbert.

(7) Barlow, T.: Congenital atelectasis, emphysema, and a cyst of the lung. *Brit. Med. Jour.*, 1880, i, 14.

(8) Bartholinus. T.: *In* Malpighii Opera Omnia, Leidener Ausgabe, 1687, Bd. ii, S. 349 u. 350. Quoted by Humbert, and Meyer.

(9) Beneke: Über Bauchlunge und Hernia diaphragmatica spuria. *Verhandl. der Deutsch. pathol. Gesellsch.*, 9. Tagung, Jahrg. 1905, 202, Quoted by Bert and Fischer.

(10) Berlin, W.: Über einen Fall von atelectatischer Bronchiektasie. *Inaug.-Dissert.*, Kiel, 1891.

(11) Bernstein, J. M.: Broncho-pneumonia with multiple cavities. *Trans. Path. Soc. Lond.*, 1905, lvi, 330–333.

(12) Bert, P., und Fischer, B.: Über Nebenlungen und versprengte Lungenkeime. *Frankf. Ztschr. f. Path.*, 1911, vi, 27–64.

(13) Biermer: Zur Theorie und Anatomie der Bronchienerweiterung. *Virchow's Arch.*, 1860, xix, 94–170; 241–287

(14) Box, C. R.: Bronchiectasis in childhood, with some observations on the condition known as honeycomb lung. *Lancet*, 1907, i, 16–19.

(15) Braun: Beitrag zur Kasuistik der Bronchiektasien im Kindesalter. *Inaug.-Diss.*, Berlin, 1886. Quoted by Edens.

(16) Buchmann, E.: Zur Lehre der fötalen Lungenatelektase und der fötalen Bronchiektase. *Frankf. Ztschr. f. Path.*, 1911, viii, 263–303.

(17) Busse: *Soc. de méd. de Greifswald*, 1902. Quoted by Humbert.

(18) Chiari, H.: Über einen neuen Typus von Missbildung an der Trachea des Menschen. *Ziegler's Beitrage zur path. Anat. u. zur. allg. Path.*, 1889, v, 329–344.

(19) *Idem*: Über ein congenitales Divertikel des rechten Stammbronchus. *Prager med. Wchnschr.*, 1890, xv, 567–568.

(20) *Idem*: *Prager med. Wchnschr.*, 1883. Quoted by Humbert.

(21) *Idem*: Über das Vorkommen eines doppelten, eparteriellen Seitenbronchus an dem Stammbronchus des Menschen. *Ztschr. f. Heilkunde*, 1890, x, 470–478.

(22) *Idem*: Über eine neue Form von "Dreitheilung der Trachea" bei einem 16-Tage alten Knaben mit sonstigen Bildungs-anomalien, darunter auch Mangel der Milz and Verlagerung des Ligamentum hepatoduodenale. *Prag. med. Wchschr.*, 1891, xvi, 89–92.

(23) Chiene, J.: Note on a supernumerary lobe of the right lung. *Jour. Anat. and Physiol.*, London, 1870, iv, 89–90.

(24) Cleland: Cause of the supernumerary lobe of the right lung. *Jour. Anat. and Physiol.*, London, 1870, iv, 200.

(25) Coats: Manual of Pathology, 1883, p. 513. Quoted by Schuchardt.

(26) Coesfeld: Über Flimmerepithelcysten des Oesophagus. *Dissert.*, Kiel, 1891. Quoted by Kern.

(27) Collins, E. W.: *Trans. Roy. Irish Acad.*, April, 1874. Quoted by Allen.

(28) Couvelaire: Dégénérescence kystique congénitale du poumon. *Rev. mens. des mal. de l'enfance*, 1904. Quoted by Sandoz.

(29) *Idem*: *Annales de gyn. et d'obst.*, 1903, lx, p. 336. Quoted by Edens.

(30) Delobel: *Gaz. hebd. de méd. et de chir.*, février, 1900. Quoted by Appel.

(31) Delobel: *Compt. rend. Soc. anatomo-clinique de Lille.* Quoted by Appel.

(32) Dionisi, A: *Lo Sperimentale*, 1903, lvii. Ref. *in Cntrlbl. f. allg. Path. u. path. Anat.*, 1904, xv, 695.

(33) Dürck, H.: Mitteilung über ein Fall von accessorischer Lunge. Münch. med. Wchnschr., 1895, xlii, 456–457.

(34) Eberth: Cyste mit Flimmerepithel in der Leber. *Virchow's Arch.*, 1866, xxxv, 478–479.

(35) Edens, E.: Über atelectatische Bronchiektasie. *Deutsch. Arch. f. klin. Med.*, 1904, lxxxi, 334–358.

(36) Edwards, W. A.: An anomalous human lung, having four lobes on the right side. *Amer. Jour. Med. Sci.*, 1885, xc, 182–186.

(37) Feustell, F.: Über die späteren Schicksale der Atelektase. *Inaug.-Dissert.*, Kiel, 1883.

(38) Fisher, T.: Dilated bronchial tubes with broncho-pneumonia in a young child. *Trans. Path. Soc. Lond.*, 1897, xlviii, 33–34.

(39) Fletcher, H. M.: Pericholangitis with cyst formation, associated with acute bronchiolectasis. *Trans. Path. Soc. Lond.*, 1901, lii, 193–199.

(40) Fontanus: Quoted by Humbert and by Meyer.

(41) Francke, W.: Über Lungenschrumpfung aus der ersten Lebenzeit. *Deutsch. Arch. f. klin. Med.*, 1894, lii, 125–143.

(42) Friedreich, N.: Cyste mit Flimmerepithel in der Leber. *Virchow's Arch.*, 1857, xi, 466–469.

(43) Froentzel: *Charité-annalen*, 1878. Quoted by Humbert.

(44) Frühwald, F.: Hernia pulmonalis aus blasiger Lungenmissbildung. *Jahrb. f. Kinderheilk.* 1885, xxiii, 418–422.

(45) Gairdner: Glasgow Path. and Clin. Society, 1885. Ref. *in* Deutsche Medicinal-Zeitung, 1886, p. 481. Quoted by Edens.

(46) Gairdner: Nothnagel's Specielle Pathologie und Therapie. Quoted by Humbert.

(47) Glur, A.: Über rudimentäre Lungenabschnitte beim Rinde. *Virchow's Arch.*, 1908, cxciv, 52–63.

(48) Gold, E.: Über Bronchuscysten und deren Entstehung. *Ziegler's Beiträge*, 1921, lxviii, 278–296.

(49) Grawitz, P.: Über angeborne Bronchiektasie. *Virchow's Arch.*, 1880, lxxxii, 217–237.

(50) Hamilton: Pathology of Bronchitis, 1883, p. 95. Quoted by Tooth.

(51) Hammar: Ein Fall von Nebenlunge bei einem Menschenfötus von 11.7 mm. Nackenlänge. *Ziegler's Beiträge*, 1904, xxxvi, 518–527.

(52) Handford, H.: An accessory lobe to left lung. *Brit. Med. Jour.*, 1885, i, 926.

(53) Heller, A.: Die Schicksale atelektatischer Lungenabschnitte. *Deutsch. Arch. f. klin. Med.*, 1885, xxxvi, 189–196.

(54) Herrmann, K.: Über eine Flimmercyste des Mediastinums. *Prag. med. Wchnschr.*, 1890, xv, 146–147.

(55) Herxheimer: Beiträge zur Kenntnis der Atelektatischen Bronchiektasie. *Breslauer ärztl. Ztschr.*, 1887. Quoted by Humbert, and by Edens.

(56) Herxheimer, G.: Über ein Fall von echter Nebenlunge. *Cntrlbl. f. allg. Path. u. path. Anat.*, 1901, xii, 529–532.

(57) Heuter, C.: Über angeborene Bronchiektasien and angeborene Wabenlunge. *Beiträge z. path. Anat. u. Path.*, 1914, lix, 520–538.

(58) Holt, L. E. and Howland, J.: The diseases of infancy and childhood, 1920, p. 75.

(59) Hondo, T.: Über congenitale Bronchiektasie. *Cntrlbl. f. allg. Path. u. path. Anat.*, 1904, xv, 129–132.

(60) Humbert, G.: De la cyanose dans les maladies congénitales du poumon. Thèse de Genève, 1903.

(61) Humbert, G.: Des malformations pulmonaires. Rev. de méd., 1904, xxiv, 453–496.

(62) Humphry, L.: Accessory lobe of the left lung. *Jour. Anat. and Physiol.*, London, 1885, xix, 345–346.

(63) Joël, J.: Ein Teratom auf der Arteria pulmonalis innerhalb des Herzbeutels. *Virchow's Arch.*, 1890, cxxii, 381–386.

(64) Kahler, O.: Über ein Divertikel des Tracheo-bronchialbaumes. *Monatsschr. f. Ohrenheilk. u. Laryngorhinologie*, 1911, xlv, 86–92.

(65) Kanthack, A. A. and Rolleston, H. D.: Report on Dr. Tooth's specimen of multiple cavities in bronchopneumonia (bronchiectasis). *Trans. Path. Soc. Lond.*, 1897, xlviii, 32–33.

(66) Kaufmann: Spez. pathol. Anatomie, 1904. Quoted by Sandos.

(67) Kern, W.: Beiträge zur Pathologie des Ösophagus. *Virchow's Arch.*, 1910, cci, 135–149.

(68) Kessler: Über mangelhafte Entwicklung der Lunge. *Inaug. -Dissert.*, Zürich, 1858. Quoted by Grawitz, and Buchmann.

(69) Kimla: I. *Compt. rend. du xii. Congrès international de médecine, Moskau*, 1897, ii, p. 161. II. Contribution à l'étude des maladies congénitales des organes glandulaires. Auszug aus einer Arbeit, die unter den "Verhandlungen der Akademie der Wissenschaften von Böhmen" 1899 erschienen ist. Quoted by Edens.

(70) Köstlin: *Arch. für phys. Heilkunde*, 1849. Quoted by Humbert.

(71) Kraus, F.: Erkrankungen der Mundhöle und der Speiseröhre. Nothnagel's Handb. d. spez. Path., 1902, xvi, Bd. i, ii Hälfte, 93–104.

(72) Lesser, A.: Quoted by Grawitz.

(73) Lewisohn, R.: Über einen Fall von echter Nebenlunge. *Cntrlbl. f. allg. Path. u. path. Anat.*, 1903, xiv, 869–877.

(74) Linser, P.: Über einen Fall von congenitalem Lungen-adenom. *Virchow's Arch.*, 1899, clvii, 281–297.

(75) Loewy, W.: Ein Fall von Pulmo succenturiatus. *Berl. klin. Wchnschr.*, 1873, x, 378.

(76) Lotmar, O.: Ein Beitrag zur Kenntnis der Schicksale der fötalen Atelektase. *Virchow's Arch.*, 1908, cxci, 28–42.

(77) Lyonnet: Case presented by Dauvergue, Soc. sciences méd. de Lyon, Séance du 4 décembre, 1902, in *Lyon méd.*, 1903, p. 253. Quoted by Humbert.

(78) MacCallum, W. G.: A textbook of pathology, second edition, 1921, p. 432.

(79) Meyer, H.: Über angeborene blasige Missbildung der Lungen, nebst einigen Bemerkungen über Cyanose aus Lungenleiden. *Virchow's Arch.*, 1859, xvi, 78–95.

(80) Mohr, R.: Über Flimmerepithelcysten des Ösophagus. *Ziegler's Beiträge*, 1909, xlv, 333–340.

(81) Muus, N.: Eine Geschwulst der Pleura, von aberrierendem Lungengewebe ausgegangen. *Virchow's Arch.*, 1904, clxxvi, 180–183.

(82) Nonnus, L.: Quoted by Meyer.

(83) Orth, J.: Beitrag zur Kenntnis des Lungenemphysems. *Berl. klin. Wchnschr.*, 1905, xlii, 1–4.

(84) Oudendal, J. A. F.: Epithelial proliferation and formation of cysts in the lungs. *Mededeel. v. d. Burg. Geneesk. Dienst.*, Eng. Ed., 1924, i, 1–24.

(85) Paul: *Mitteilung aus den Hamburgischen Staatskrankenanstalten*, 1899, p. 285. Quoted by Edens.

(86) Pepere, A.: Della degenerazione cistica del pulmone. *Lo Sperimentale*, 1906, lx, 171–196.

(87) Pozzi: Note sur les lobes surnuméraires du poumon droit de l'homme et en particulier sur une anomalie réversive (existence d'un lobus impar). *Revue d'anthropologie*,

Paris, 1872, i, 443. Quoted by Lewisohn.

(88) Quenzel: *Nordiskt med. Arch.*, 1900, No. 8. Quoted by Lewisohn.

(89) Rau, F.: Flimmerepithelcyste des Ösophagus. *Virchow's Arch.*, 1898, cliii, 26–29.

(90) von Recklinghausen: Handbuch der allgem. Path. des Kreislaufs und der Ernährung, 1883, S. 315. Quoted by Schuchardt.

(91) von Recklinghausen, F.: Über die Ranula, die Cyste der Bartholin'schen Drüse und die Flimmercyste der Leber. *Virchow's Arch.*, 1881, lxxxiv, 425–495.

(92) Reisinger, L.: Beitrag zur Kenntnis des chronischen Bronchitis und Bronchopneumonie des Rindes. *Monatshefte f. prakt. Tierheilk.*, xix, 193–08 Quoted by Glur. .

(93) Rektoržik: Über accessorische Lungenlappen. *Wchenbl. d. Ztschr. d.k.k. Gesellsch. d. Aerzte in Wien*, 1861, xii, 4. Quoted by Wechsberg, and by Lewisohn.

(94) Ribbert, H.: Noch einmal das Traktiondivertikel des Ösophagus. *Virchow's Arch.*, 1906, clxxxiv, 403–413.

(95) Rindfleisch: Über cirrhosis cystica pulmonum. *Verhandl. d. Gesellschaft deutscher Naturforscher und Ärzte*, 1897, lxix, zweiter Theil, II. Hälfte, 22–24.

(96) Rohmer u. Borchert: Ein Fall von Verschluss des Hauptbronchus mit Lungenschrumpfung. *Deutsch. Arch. f. klin. Med.*, 1897, lix, 585–597.

(97) Rokitansky, K.: *Muscalpräparat Nr. 2927, path.-anat. Institute in Wien.* Quoted by Stoerk.

(98) Rokitansky. K.: Lehrbuch der spec. pathol. Anatomie, 1861, Bd. iii, 44 u. 56. Quoted by Stoerk.

(99) Rokitansky, K.: *Österr. med. Jahrb.*, 1838, xvi. Quoted by Gold.

(100) Ruge, C.: *Berl. klin. Wchnschr.*, 1878, xv, 401.

(101) Sandoz, E.: Über zwei Fälle "fötaler Bronchiektasie." *Ziegler's Beiträge*, 1907, xli, 495–516.

(102) Schaffner, G.: Über den Lobus inferior accessorius der Menschlichen Lunge. *Virchow's Arch.*, 1898, cli, 1–25.

(103) Schlicht: Ein Fall von Missbildung beiden Lungen. *Münch. ärztliche Intelligenzbl.*, 1885. Quoted by Humbert.

(104) Seltsam, A.: Über einen weiteren Fall von abdomineller Nebenlunge. *Virchow's Arch.*, 1905, clxxx, 549–552.

(105) Sharkey, S. J.: Acute bronchiectasis. *St. Thomas's Hosp. Reports*, 1892–93, xxii, 33–36.

(106) Sottas, J.: Dilatation bronchique exclusivement limitée au lobe supérieur du poumon droit, hyperplasie considérable des fibres musculaires lisses. *Bull. Soc. anat. de Paris*, 1891, lxvi, 376–378.

(107) Springer: Rudimentäre accessorische Lunge. *Prag. med. Wchnschr.*, 1898, xxiii, 393–395.

(108) Stilling, H.: Eine Flimmercyste des Mediastinum anticum. *Virchow's Arch.*, 1888, cxiv, 557–560.

(109) Stoerk, O.: Über angeborene blasige Missbildung der Lunge. *Wien. klin. Wchnschr.*, 1897, x, 25–31.

(110) Sutherland, G. A.: *In* "Diseases of Children," edited by Garrod, Batten and Thursfield, 1913, p. 340.

(111) Thomas: Beitrag zum Studium der späten Form der Blausucht, peripherischen Ursprungs. *Ztschr. f. klin. Med.*, 1900. Quoted by Humbert.

(112) Tillaux: Communication sur une tumeur gazeuse de la plèvre. *Bull. Soc. anat.*, 1860, 2e série, t. vi. Quoted by Appel.

(113) Tooth, H. H.: Multiple cavities in broncho-pneumonia. *Trans. Path. Soc. Lond.*, 1897, xlviii, 30–32.

(114) Trespe: Flimmerepithelcyste der hinteren Ösophaguswand. Arbeiten aus dem Path. Institute Posen, herausgegeb. von Lubarsch. Wiesbaden, 1901. Quoted by Bert and Fischer.

(115) Valisneri: Quoted by Meyer.

(116) Virchow: Zur Entwicklungsgeschichte des Kretinismus und der Schädeldeformitäten. Gesammelte

Abhandlungen, S. 982. Quoted by Sandoz, and Grawitz.

(117) Virchow, R. u. Heubner: Bronchiektasie bei einem ganz jugendlichen Kinde. *Berl. klin. Wchnschr.* 1898, xxxv, 66–67.

(118) Virchow, R.: Teratoma myomatodes mediastini. *Virchow's Arch.*, 1871, liii, 444–454.

(119) Vogel, R.: Zwei Fälle von abdominalem Lungengewebe. *Virchow's Arch.*, 1899, clv, 235–255.

(120) Voisin: Sur un cas de lobe erratique du poumon. *Arch. de méd. expér. et d'anat. pathol.*, 1903, xv, 228. Quoted by Bert and Fischer.

(121) Wechsberg, F.: Über eine seltene Form von angeborener Missbildung der Lunge. *Cntrlbl. f. allg. Path. u. path. Anat.*, 1900, xi, 592–599.

(122) Winslow: Quoted by Meyer.

(123) Wollmann: Ein Fall von Agenesie der linken Lunge mit Bronchiektasie. *Inaug. Dissert.*, Freiburg, 1891. Quoted by Humbert.

(124) von Wyss, H.: Zur Kenntnis der heterologen Flimmercysten. *Virchow's Arch.*, 1870, li, 143–144.

(125) Zahn, F. W.: Über mit Flimmerepithelien ausgekleidete Cysten des Ösophagus, der Pleura und der Leber. Beitrag zur Lehre von den angeborenen Mucoidcysten. *Virchow's Arch.*, 1896, cxliii, 170–187.

(126) Zipkin, R.: Über ein Adeno-rhabdomyom der linken Lunge und Hypoplasie der rechten bei einer totgeborenen Frucht. *Virchow's Arch.*, 1907, clxxxvii, 244–264.

Books Received

The Nature of Enzyme Action. By Sir W. Bayliss, M.A., D.Sc., F.R.S. Fifth edition, 1925. 8°. 200 pages. Longmans, Green and Co., New York; Toronto. $3.25.

Pediatrics. By Various Authors. Edited by Isaac A. Abt, M.D. Volume vii, with 70 illustrations. 1925. 8°. 879 pages. W. B. Saunders Company, Philadelphia and London. $10.00.

Modern Surgery, General and Operative. By John Chalmers DaCosta, M.D., LL.D., F.A.C.S. Ninth edition, revised and reset with 1200 illustrations, some in colors. 1925. 8°. 1527 pages. W. B. Saunders Company, Philadelphia and London. $10.00.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Edited by Mrs. H. M. Mellish. Volume xvi, 1924. 8°. 1331 pages. 1925. W. B. Saunders Company, $13.00.

Physical Diagnosis of Diseases of the Chest. By Joseph H. Pratt, M.D. and George E. Bushnell, Ph.D., M.D. With 166 illustrations. 1925. 8°. 522 pages. W. B. Saunders Company, Philadelphia and London.

An Introduction to Sexual Physiology. For Biological, Medical, and Agricultural Students. By F. H. A. Marshall, F.R.S. With illustrations. 1925. 8°. 167 pages. Longmans, Green, and Co. New York and London. $2.75.

Approaching Motherhood. Questions and Answers of Maternity. By George L. Broadhead, M.D. 1925. 12°. 193 pages. Paul B. Hoeber, New York. $1.25.

The Principles of Public Health Engineering. By Earle B. Phelps, B.S. 1925. 8°. 265 pages. The Macmillan Company, New York.

Simplified Nursing. By Florence Dakin. R.N. Illustrated. Lippincott's Nursing Manuals. [1925.] 8°. 499 pages. J. B. Lippincott Company, Philadelphia, London, Montreal. $3.00.

A Synopsis of Gynaecology. By Arthur Gray, F.R.C.S., M.R.C.P. 1925. 12°. 352 pages. Edward Arnold & Co., London.

Hand-Atlas of Clinical Anatomy. By A. C. Eycleshymer, B.S., Ph.D., M.D., and Tom Jones, B.F.A. With special dissections by O. E. Nadeau, B.S., M.D. Illustrated with 395 line drawings, mostly in colors. 1925. 4°. 424 pages. Lea & Febiger, Philadelphia and New York. $10.00.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D. with the collaboration of Chas. H. Mayo, M.D. Thirty-fifth series, volume ii, June, 1925. 8°. 311 pages. J. B. Lippincott Company, Philadelphia and London. $2.00.

Pneumonia: Its Pathology, Diagnosis, Prognosis and Treatment. By the Late R. Murray Leslie, M.A., B.Sc., M.D. Edited and revised by J. Browning Alexander, M.D., M.R.C.P. (Lond.) 1924. 8°. 351 pages. William Heinemann, London. 12/6 net.

The Newer Knowledge of Nutrition. The Use of Foods for the Preservation of Vitality and Health. By E. V. McCollum, Ph.D., Sc.D., and Nina Sim-

MONDS, Sc.D. (Hygiene). Third edition entirely rewritten illustrated. 1925. 8°. 675 pages. Macmillan Company, New York.

The George Blumer Edition of Billings-Forchheimer's Therapeusis of Internal Diseases. Care and Management of Maladies and Ailments Other than Surgical. Six volumes and desk index. 1925. 8°. D. Appleton and Company, New York and London. $52.50 for the set.

Diseases of the Ear, Nose and Throat. By HAROLD HAYS, M.A., M.D., F.A.C.S. Illustrated with 495 half-tone and line engravings in the text, and 55 full page plates, nearly all in colors. 1925. 8°. 961 pages. F. A. Davis Company, Philadelphia. $10.00 net.

Diabetes. Its Treatment by Insulin and Diet. A Handbook for the Patient. By ORLANDO H. PETTY, A.M., M.D., F.A.C.P. and WILLIAM H. STONER, A.M., M.D., F.A.C.P. With illustrations and tables. 1925. 12°. 133 pages. F. A. Davis Company, Philadelphia. $1.50 net.

Pediatrics of the Past. An Anthology. Compiled and edited by John Ruhräh, M.D. With a foreword by Fielding H. Garrison, M.D. With fifty-four text illustrations and eighteen full page plates. 1925. 8°. 592 pages. Paul B. Hoeber, New York. $10.00.

The Fats. By J. B. LEATHES, M.A., M.B., F.R.S., and H. S. RAPER, C.B.E., M.B., Ch.B., D.Sc. Second edition. Monographs on Biochemistry. 1925. 8°. 242 pages. Longmans, Green and Co., London. $4.50.

The Cerebro-Spinal Fluid in Clinical Diagnosis. By J. GODWIN GREENFIELD, M.D., M.R.C.P., and E. ARNOLD CARMICHAEL, M.B., Ch.B. 1925. 8°. 272 pages. Macmillan and Co., London.

Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie. Ein Handbuch für Ärzte. Von PROFESSOR A. D. CZERNY und PROFESSOR A. KELLER. Zweite vollkommen umgearbeitete Auflage. II. Band, I. Teil. 1925. 8°. 368 pages. Franz Deuticke, Leipzig und Wien.

Psychoanalysis and the Psychic Disorder of General Paresis. By STEFAN HOLLÓS and S. FERENCZI. Authorized English, by Gertrude M. Barnes and Günther Keil. Nervous and Mental Disease Monograph Series No. 42. 1925. 8°. 48 pages. Nervous and Mental Disease Publishing Company, New York and Washington. $1.50.

Diseases of the Bronchi, Lungs, and Pleura. By FREDERICK T. LORD, M.D. Second edition, thoroughly revised, with the addition of a chapter on pulmonary tuberculosis. Illustrated with 107 engravings and 3 colored plates. 1925. 8°. 776 pages. Lea & Febiger, Philadelphia and New York. $8.00.

Pediatric Nursing. A Text-Book for Nurses. By ABRAHAM LEVINSON, B.S., M.D. Illustrated with 27 engravings and 1 colored plate. 1925. 12°. 251 pages. Lea & Febiger, Philadelphia and New York. $2.50.

The Chemistry of the Blood in Clinical Medicine. By O. L. V. DE WESSELOW. M.B. (Oxon), F.R.C.P. (Lond.) 1925. 8°. 255 pages. William Wood & Company, New York. $4.50.

College of Physicians of Philadelphia. Transactions. Third Series. Volume the Forty-Sixth, 1924. 892 pages. 8°. Printed for the College. Philadelphia.

The Mechanism and Graphic Registration of the Heart Beat. By SIR THOMAS LEWIS. M.D., F.R.S., F.R.C.P., D.Sc., C.B.E. 3rd edition. 529 pages. 8°. Shaw & Sons Ltd., London. 1925. $12.00.

Cancer and the Public. The Educational Aspect of the Cancer Problem. By CHARLES P. CHILDE. B.A., F.R.C.S., M.R.C.P.E. 267 pages. 8°. E. P. Dutton and Company, New York, 1925. $4.25.

The Ophthalmic Year Book. Volume xxi. Containing Bibliographies, Digests and Indexes of the Literature of Ophthalmology for the year 1924. Edited by WILLIAM H. CRISP. Ten Illustrations in the Text. Ophthalmic Publishing Company, Chicago. 1925.

A Text-Book of General Bacteriology. By EDWIN O. JORDAN, Ph.D. Fully illustrated. Eighth edition, thoroughly revised. 752 pages. 8°. W. B. Saunders Company, Philadelphia and London. 1924. $5.00.

The American Illustrated Medical Dictionary. A New and Complete Dictionary of the terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S. Thirteenth edition, revised, and enlarged. 1344 pages. 8°. W. B. Saunders Company, Philadelphia and London. 1925. $7.50.

Physical Chemistry in Biology and Medicine. By J. F. MCCLENDON, Ph.D., and GRACE MEDES, Ph.D. 1925. 8°. 425 pages. Illustrated. W. B. Saunders Company, Philadelphia and London. $4.50.

Preventive Medicine. By MARK F. BOYD, M.D., M.S., C.P.H. 1925. 8°. 429 pages. Second edition revised. W. B. Saunders Company, Philadelphia and London. $4.00.

Book Reviews

Pediatrics of the Past. By JOHN RUHRÄH. 592 pp. $10.00. (*Paul B. Hoeber, Jr., New York.*)

To relatively few of us is the good fortune granted to possess any of the original editions of the writings of famous physicians who have gone before us, and no one can hope to gather even an approximately complete collection of manuscripts and early printed books dealing with any branch of medicine in by-gone ages.

The author of this book is to be congratulated on having rendered a service to the medical profession. In the pages of his anthology, for such it is, are to be found reprinted, together with short biographies, characteristic passages from the original works of the more important authors who have written on the disease of children from the middle of the fifteenth to the middle of the nineteenth century. In many cases short tracts have been reprinted entire. While the primary purpose of the author was apparently to create an anthology of the diseases of children from the advent of the printing press to the present, some few of the ancients receive cursory attention at the beginning of the book. A few pages are devoted to the pediatrics of Hippocrates, and to the Roman and Byzantine Greeks, Soranus, Aretaeus of Cappadocia, Aetius, Oribasius and Paul of Aegina.

It is, however, to the pediatric incunabula (of Bagellardus, Metlinger and Roelans) that Dr. Ruhräh has given his best, and it is the part of the book in which they and the pediatrists of the early renaissance are are dealt with which is the best and most valuable.

"Pediatrics of the Past" represents a large amount of labour in searching out, reading and translating original sources. Dr. Ruhräh has resurrected the dead past not to display and mock its naked obscenities or to hold to ridicule its weaknesses and its errors, but with real affection to make it possible for others to appreciate its excellencies. He has brought back the forgotten worthies of an earlier medicine to applaud their skill and to admire their acumen.

The book is a good book and one will be a better physician for having read it.

P. G. S.

Normal Bones and Joints. By ISADORE COHN. 218 pp. $10.00. (*Paul B. Hoeber, Jr., New York.*)

This volume appears as the fourth of a series of ten monographic atlases known collectively as the Annals of Roentgenology.

In an atlas of this sort the illustrations are of major importance. The excellence of the text is a secondary matter. The book is well gotten up and the text is clear and readable. It is a matter much to be regretted that expense in this country precludes the possibility of illustrating works like the one under consideration with photographic prints made directly from the original plates. Those who are familiar with Continental atlases and journals illustrated in this way will always regret the impossibility of their duplication in America.

It has always seemed to the writer that the illustrations in atlases of X-ray pictures should be reproduced as negatives, not only because we are accustomed to read the negative plate but because there is less loss of detail in the process of rephotographing and making half tones when the shadows are shown as white on black than vice versa. Nevertheless, the plates in this book are well done; indeed they are far above the average.

The author has illustrated and briefly described the development and anatomy of the bones and joints chiefly from the point of view of their surgical application and has laid stress on the importance of correct interpretation of the normal configuration in order that failures in diagnosis of epiphyseal separation and fractures may be minimized.

It is quite apparent that the book as it stands is in a great measure the record of the author's own personal experience. The various important lesions are well illustrated by the inclusion of characteristic case histories.

P. G. S.

The Newer Knowledge of Nutrition. Third edition. By E. V. McCollum and N. Simmonds. 675 pp. $4.25. (*McMillan Company, New York.*)

Those who are familiar with the first two editions of this work will welcome the appearance of the third. Originally a small duodecimo volume, the advance guard of a host of tractates on vitamines, and their function in the field of nutrition, the volume has grown to a reference textbook of some pages dealing with all the recent work on the feeding of man and animals. The book includes the discussion of the advances most recently reported in the literature of this field, and since this literature has even in the last few months grown with tremendous rapidity, the revision of the second edition to produce the third must have been a task involving a vast amount of labour.

The critical discussion of the investigations mentioned in the book are excellent. The chapter on rickets has been brought up to date and contains all of the newer work on actinotherapy besides other laboratory and clinical investigation. This chapter and the work on scurvy as well as the discussion of goitre and diabetes are of immediate and practical interest to the practitioner of medicine.

This work is one which should be carefully studied by anyone who plans to undertake any investigation in nutrition and should be read with care by physicians, dietitians, etc., who are brought into contact with feeding problems. Moreover, it is sufficiently readable to permit a layman to acquire readily much valuable information.

The professional investigator will be amply repaid for its perusal by being furnished with a complete survey of nutrition in succinct form and a carefully constructed and complete bibliography of the subject.

P. G. S.

Treatment of Fractures in General Practice. By C. M. Page and W. R. Bristow. 239 pp. $4.00. Oxford Medical Publications. (*H. Frowde and Hodder & Stoughton.*)

This excellent volume of the useful series of Oxford Medical Publications fulfills a very practical purpose, bringing together the main facts of importance about fractures in general and making them clear in a simple readable way. The general principles of treatment are pointed out and the various dangers and pitfalls clearly marked. The sections on delayed union, non-union and ischaemic contractures are concise and to the point.

The most valuable contributions to the general subject are; first, the insistence on the usefulness of prolonged traction intelligently applied as shown by war experience, and secondly, the incorporation of sound orthopaedic principles, clearly demonstrated, in a book of this character which is admittedly for the use of the general practitioner. The special sections dealing with the individual types of fracture are well illustrated and a satisfactory method of reduction and treatment is definitely outlined.

Quite wisely one good form of treatment is described and little space wasted in discussion of alternative methods. In certain regions, however, the form of treatment given is not the one that we have found most convenient, but the choice of method is always in itself quite sound, and it is certainly true that one good method well understood is better than half a dozen equally good ones imperfectly understood and consequently unsatisfactorily applied. The treatment advised is uniformly conservative and operation resorted to only in the classical instances, such as fracture of the patella, etc.

Reference to a few minor points, to which we feel exceptions can be taken, may be omitted in view of the general soundness and excellence of the book. The clearness, conciseness and definiteness with which the authors have handled their difficult subject make the book one of marked value to the busy practitioner who finds fractures a source of worry and at times of

despair. It is not a book which should form the sole background for a student's acquaintance with fractures, but it will by its very serviceableness doubtless displace lengthier and weightier tomes from many a practicing doctor's desk.

R. W. J., Jr.

Lumbar Puncture. Its Anatomical and Physiological Relations. Technique. Method of Investigations. Diagnostic Value and Therapeutical Applications. By Martin Pappenheim. Translated by George Caffrey. Cloth. 248 pp. $5.00. (*William Wood & Co., New York, 1925.*)

A great deal of valuable information has been compressed by the author into this small volume. In the first chapter the physiology of the cerebrospinal fluid, the anatomical relations of the ventricular and subarachnoid spaces are briefly summarized, and the technique and dangers of lumbar puncture are fully discussed. The determination of spinal fluid pressure together with the sources of error are considered in the 4th and 5th chapters. Many different methods for the quantitative and qualitative study of spinal fluid cells are given. Chemical analysis, especially the determination of the protein constituents, is adequately presented. One chapter is devoted to the colloidal gold reaction and its substitutes. The theory and methods of carrying out the Wassermann reaction and the precipitation tests for syphilis are discussed, but no mention is made of Kolmer's modified technique. There are good chapters on the diagnostic, prognostic and therapeutic importance of lumbar puncture.

In an appendix there is a very inadequate description of the methods of "encephalography" as advocated by "Bingel" and "Weigeldt." Dandy's name is mentioned only once. Eskuchen's technique for cistern puncture is given, but Ayres' work is not mentioned.

References to some 200 German works are given. Only three references to English articles are to be found. There is a good index. The book is well bound and clearly printed.

F. R. F.